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CONTENTS

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EDITORIAL

Welcome to the July/August 2009 issue of HTB that includes our first coverage from the IAS conference held in Cape Town in July.

Probably the most important results come from the UK MRC-sponsored DART trial. We summarise the main results and encourage readers to see full details from the many posters and presentations that are posted to the study website.

http://www.ctu.mrc.ac.uk/dart

We also include reports from the Clinical Pharmacology Workshop held earlier in the year that received very little media coverage and include the best coverage on basic science news from Richard Jefferys blog.

Swine flu in the UK

We lead this issue by including a resource developed by Birmingham Heartlands Hosptial to help triage patients with suspected symptoms of swine flu.

The is not an 'evidence-based' resource but reproduced as an example of best practice that may help other clinics develop their own responses. The resource includes a flow diagram for managing patient calls, and we include a similar diagram used by the Chelsea and Westminster Hospital in London, as a second example.

Thanks to both hospitals for producing early resources. Both clinics emphasise that these have been produced only for use in their own patients.

For patients, i-Base posted a summary of Q&As on the i-Base website in July, and we reprint an updated version in case it is useful to photocopy.

This new draft (august 2009) has two important updates:

i) That antiviral flu medications such as oseltamivir (Tamiflu) are now distributed via the national flu pandemic phoneline service (0800 1513 100/200); and

ii) That maintaining the supply of antiretroviral medications in London (and likely other clinics) is to be now likely to be managed by ensuring that patients have sufficient ARVs to last through to January.

This will minimise the need for most patients to visit their HIV clinic visits during the likely peak flu period (October/November). It will also ensure that if services are distrupted, including if clinics are forced to close for short periods, that patients have sufficient meds to last until they are resumed again.

Some clinics are prescribing an additional month's supply of meds that should not be used until the flu concern is over. Other clinics may use different protocols.

All patients are to be advised to always keep ONE MONTHS SUPPLY of meds in case of this potential disruption and to arrange for their Autumn /Winter prescriptions in advance during August or September.

This is to ensure that no patient needs to interrupt treatment due to drug supply problems.

SWINE FLU EPIDEMIC

HIV swine flu telephone triage tool

The following resource was developed by Birmingham Heartlands Hospital and is to be used with flow diagram 'HIV and Influenza H1N1v'. This is an empirical protocol drawn up by individuals with some experience in the recent UK swine flu outbreak. Modifications have been made following a meeting at the HIV/ IAS conference 2009 in July. This is just one suggested clinical approach.

Please use and adapt this to your own clinic, if you would like to suggest improvements or share experiences please contact:

steve.taylor@heartofengland.nhs.uk

As they are produced, updated drafts will be posted online:

http://www.sexualhealthbirmingham.co.uk

At the IAS meeting we heard that no country, so far, appears to have seen significant numbers of complicated cases of swine flu in their HIV-positive populations. This was communicated by clinicians from New York, Canada, the UK and Mexico.

Inquiry re HIV and swine flu: a suggested approach

- Does the patient have symptoms consistent with **"typical" flu**?

FLU DIAGNOSTIC CRITERIA

- An acute-onset illness with history of feeling feverish and confirmed temperature >38°C
- AND flu-like illness (two or more of the following symptoms: cough, sore throat, runny nose, limb/joint pain, headache)
- Significant diarrhea has also been described by several clinicians

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- If they fulfil the above criteria but have none of the conditions * or symptoms ** listed below, then advise the patient that they may be suffering from flu. Treatment can be obtained by calling the pandemic flu service line on 0800 1513 100 / 0800 1513 200 or visiting the website:

  http://www.direct.gov.uk/pndemicflu
- They should be advised NOT to attend hospital unless they deteriorate, or if symptoms **fail to improve** within 48 hours of commencing flu antivirals, when they should be clinically assessed.
- Reassure them that it's appears safe to take antiretrovirals (ART) with flu antivirals e.g. oseltamivir (Tamiflu).
- Although there is the potential for drug interactions between ART and osteltamivir we have taken the approach that potential benefits exceed the potential for side effects. Obviously this can be modified as new data emerges.
- The theoretical interactions with renally excreted drugs and osteltamivir have led us to recommend that if patients have significant renal impairment (ie eGFR <40 mL/min) **inhaled Zanamivir can be considered as an alternative** (see below).
- In pregnancy we have recommended **inhaled Zanamivir (Relenza)**. However systemic treatment should not be withheld if the clinical condition warrants treatment. (Deaths have occurred in pregnant women who maybe at greater risk of severe infection).
- Reassure the patient that most people with uncomplicated flu will be significantly better within 48hours.
- Alternatively persons with severe symptoms that are not classically flu-like should be assessed and have flu swabs performed since a negative test can be very informative.

If the patient meets the flu diagnostic criteria above **AND** has any of the following conditions* then they need to be assessed by the ID/HIV/GU registrar on call for the day _____ : [INSERT APPROPRIATE NUMBER]

*** Conditions requiring assessment by a registrar:**

- Pregnancy (any trimester)
- Asthma and other chronic lung disease
- Morbid obesity
- Significant immune suppression

Note: We suggest assessing patients with CD4 counts <200 or CD4% <15% with symptoms as they may have an alternative non-flu diagnosis. These cases should be discussed with a senior member of the HIV team or the ID /HIV/GUM registrar on call.

If the patient meets the flu diagnostic criteria above, but also has any of the following symptoms** they should be assessed by the ID/HIV/GUM registrar on call for the day **immediately**.

**** Additional symptoms requiring immediate assessment**

- Significant breathlessness or patient is unable to complete sentences
- Hypoxia <94% on air
- Unable to tolerate oral fluids or has significant vomiting
- Confusion
- Hypotension systolic BP <90
- If the patient has already received flu antivirals and is not showing signs of improvement **after** 48 hours or is feeling worse.

Flow diagram A: HIV and Influenza H1N1v (Birminham Heartlands Hospital)

HIV patients may come into contact with hospital services in various ways. Flow diagram A outlines a suggested protocol for 2 of a common scenarios: telephone contact to members of the HIV team or unplanned presentation to HIV/ID/GUM outpatient clinics.

Treatment

- Flu antivirals should be obtained by the patients calling the **pandemic flu service line** on 0800 1513 100 / 0800 1513 200 or visiting the website:

  http:www/direct.gov.uk/pandemicflu

- **Oseltamivir (Tamiflu)** is the currently recommended first-line flu antiviral for most HIV patients and it should be commenced immediately. The dose is 75 mg bd for 5 days.
- In patients with significant renal impairment (eGFR <40 ml/min) or **pregnant** women we would consider using **inhaled zanamivir (Relenza) as an alternative.** However, If symptoms are significant, discussion should be sought with senior member of the HIV team with regards to the use of osteltamivir.
- **Inhaled zanamivir**: Two 5mg blisters are to be inhaled (using the 'Diskhaler') twice a day for at least five days (equivalent to 10mg twice a day for five days). The patient needs to be capable of using disk haler for administration.
- If intolerant of zanamivir, **oseltamivir** may be used with caution +/- dose modification. For further information contact ID/ HIV/GU registrar on call [INSERT NUMBER AND BLEEP].

Prophylactic/post exposure treatment

- For HIV positive patients with CD4 > 200 or ≥15% we **would not** routinely recommend prophylaxis but instead suggest standard treatment **IF** the patients develops symptoms and meets the flu criteria above.
- For HIV positive patients with CD4 <200 or ≤14% prophylaxis may be considered in cases of significant exposure. However to date there is no data to suggest that these individuals are at increased risk of severe disease.
- Please remember in patients with CD4 counts <200 or ≤14% other opportunistic infections may present with flu like symptoms and patients should have diagnostic swabs to aid diagnosis and be discussed with a senior HIV doctor or ID/HIV/GUM SPR on call.
- For a usable definition we have classified **significant exposure** as sitting <1 metre from an infected individual for >1 hr.
- The **oseltamivir** (Tamiflu) dose when used as prophylaxisis 75 mg od for 10 days.
- **Inhaled zanamivir**: Two 5mg blisters are to be inhaled (using the 'Diskhaler') once a day for **at least ten days** (equivalent to 10mg twice a day for five days) The patient needs to be capable of using diskhaler administration.

Diagnostic swabs for influenza

- Although swabbing is now not routinely being performed we would advocate taking swabs in individuals infected with HIV as knowledge of negative results may be useful. The patient does not have to attend hospital for this and can be organised via GP or flu treatment centres.

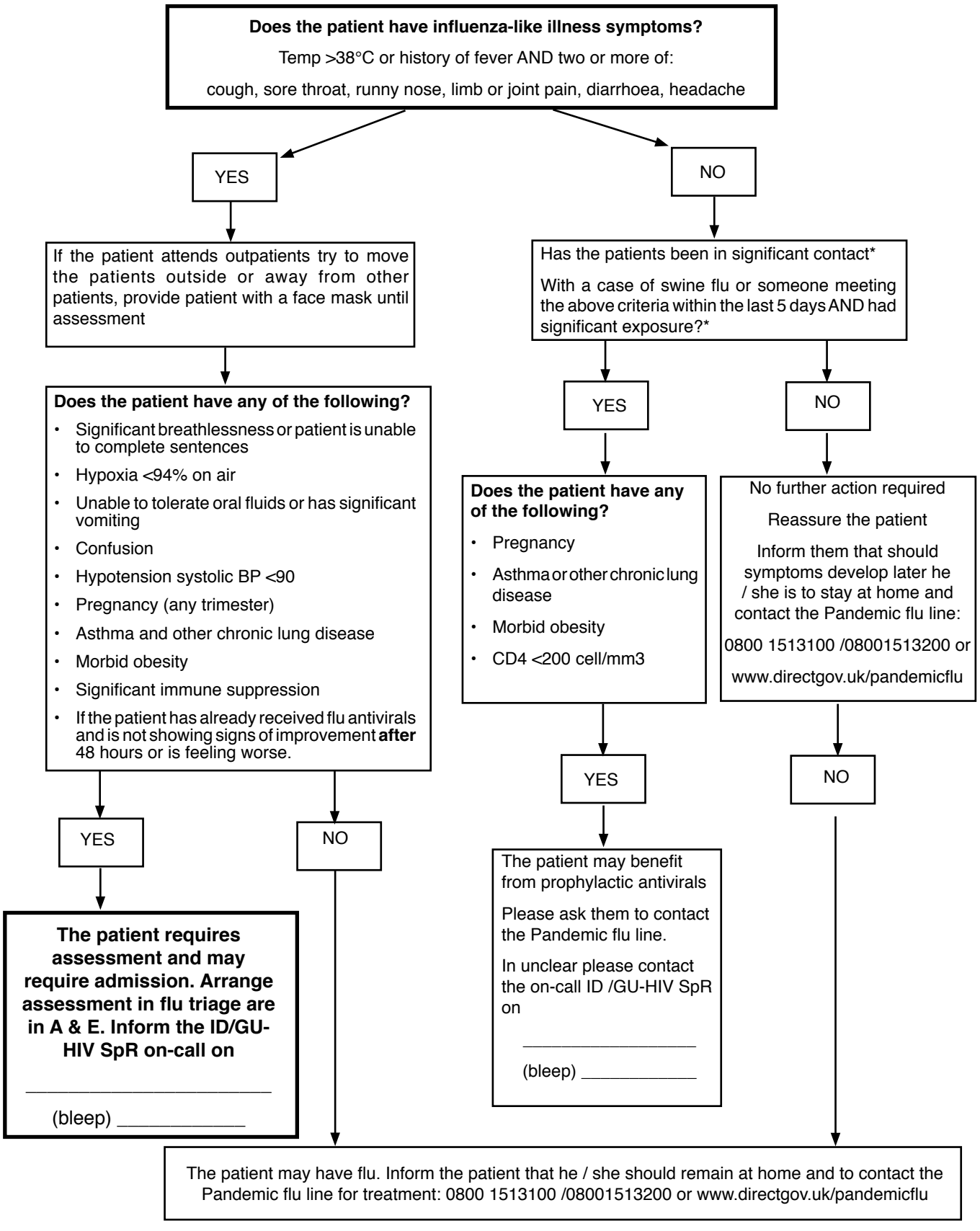
Flow diagram B (Chelsea and Westminster Hospital, London)

The second example flow diagram was produced for managing patients at the Chelsea and Westminster Hospital in London.

A caution with this option is that a patient with a life-threatening condition who thought they had flu could end up going down the left-hand 'no further action' route. The standard government advice on risk factors (eg. chronic heart, renal, liver, neurological disease), is non-evidence-based and may not be relevant in this (or possibly any) flu outbreak. It also does not address exposure

Example 1: Flow diagram A (Birmingham Heartlands Hospital)

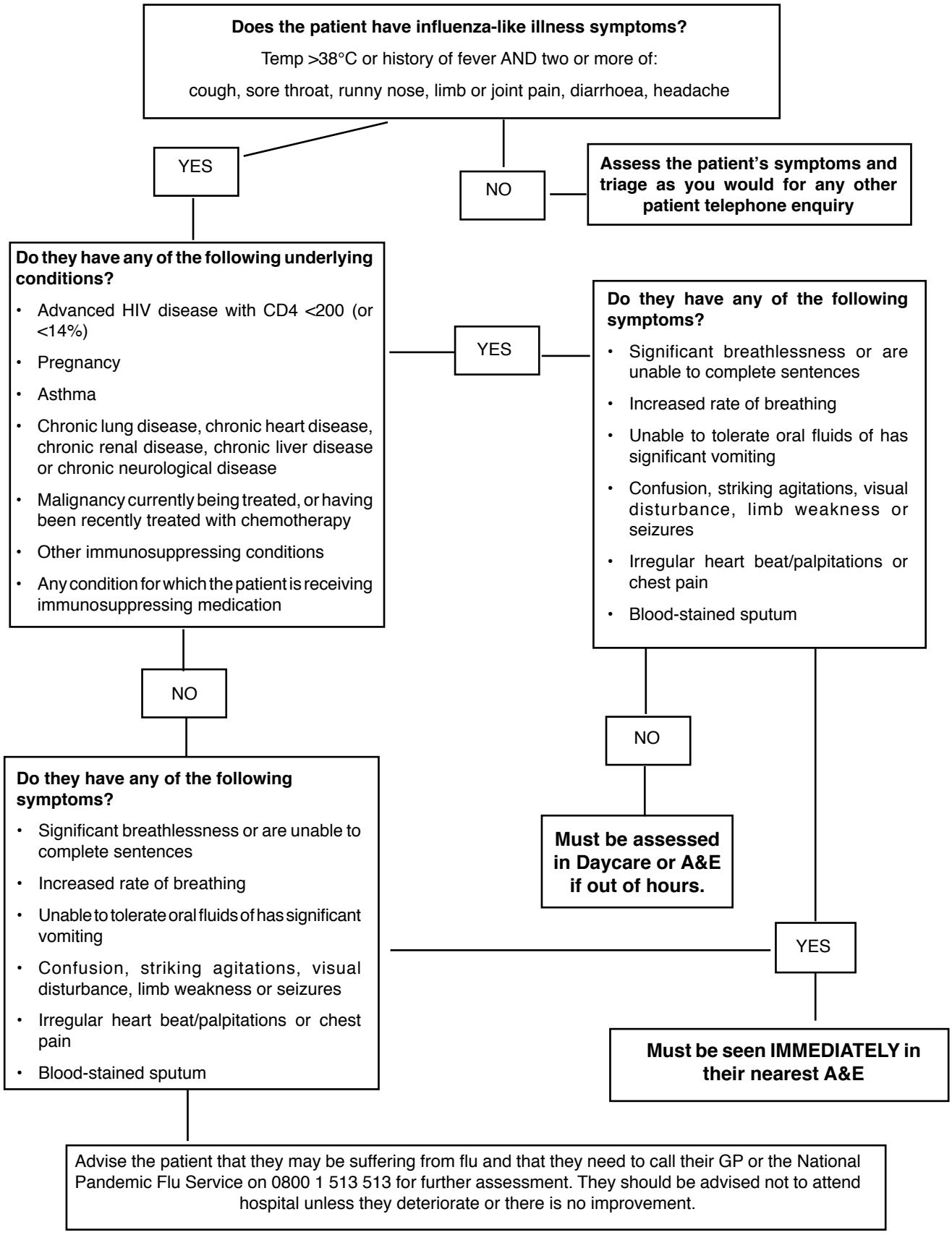
Telephone call re: swine flu from a worried HIV patient or patient attends HIV /ID/GUM outpatients reception seeking advice (Draft 3, July 2009).



* **Significant exposure** defined as "as sitting <1 metre from an infected individual for >1 hr".

Example 2: Flow diagram B (Chelsea and Westminster Hospital, London)

The flow diagram was produced for managing patients at the Chelsea and Westminster Hospital in London.



i-Base Q&A: swine flu and HIV in the UK

Q. What is swine flu?

A. Swine flu is a new strain of flu (influenza). The medical name for this strain is H1N1v. It has been called a 'pandemic' because of the speed with which it spread to many different countries in a short time.

Q. Are HIV-positive people more at risk of catching swine-flu?

A. No. Generally, as with other strains of flu, having HIV does not increase your risk of catching swine flu.

Q. Are HIV-positive people at risk of becoming more ill from swine flu?

A. Not generally. It may be more serious if you have a low CD4 count (less than 200 cells/mm3). This is mainly because symptoms of other serious infections could be mistaken for flu. ***If you have flu symptoms and either a low CD4 count, other health complications or are pregnant, please call your HIV clinic.***

Q. How is swine flu different from regular seasonal flu?

A. Because this is a new strain of flu virus, no-one is currently immune. Researchers are already working to produce a vaccine, and this may, or may not, be ready in time for the next flu season.

Q. How is swine flu spread?

A. Swine flu is spread by person-to-person contact, just like regular flu - specifically through not covering your mouth when sneezing and not washing your hands.

Catch-it, Bin-it, Kill-it. (www.nhs.uk)

Q. Will flu meds work in people who are HIV-positive?

A. Antiviral medications used to treat flu (for example, oseltamivir (Tamiflu) and zanamivir (Relenza) will work in HIV-positive people. The main reson to take them is to reduce how infectious you are.

Q. Will flu treatments interact with my HIV drugs?

A. There is a potential for interactions between Tamiflu, boosted PIs and some nukes (3TC, FTC and tenofovir) but the benefits outweigh this small risk. Your pharmacist will advise you on this. *

Q. Will I still get my HIV meds?

A. If the flu outbrteak is severe this could limit routine services. To prepare for this ALWAYS KEEP AT LEAST ONE MONTH'S SUPPLY of HIV meds at home. Some clinics will give you an additional month supply or ask you to return earlier for a new prescription. During August or September, arrange to get enough meds to last you until January. You want to avoid having to visit your clinic in October or November when the flu outbreak is likely to be at it's peak.

Q. What do I do if I think I have symptoms?

A. If you have internet access see:

http://www.direct.gov.uk/pandemicflu

If you have symptoms call:

0800 15 13 100

This is the number to access flu meds. You should get these if you are HIV-positive.

Do not visit your GP, hospital or clinic unless you have been advised to.

Q. When does seasonal flu occur?

A. The risk period for flu, including swine flu, is during the autumn and winter, especially from September to December.

Q. What is the risk that this years' flu will be swine flu and be more severe?

A. This is difficult to predict. Hopefully, there is only a small chance of such a serious outbreak this year.

Q. Should I have the flu vaccine?

A. HIV-positive people are routinely recommended to have the seasonal flu vaccine. You need to be registered with a GP to get this and any new vaccinations. Your clinic can help with this or see:

www.nhs.gov.uk

Q. Where can I get more information?

A. The NHS website will provide updates. Your doctor and clinic will have specific information too. See also:

i-Base: 0808 800 6013 (Mon, Tues, Wed 12-4pm). www.i-Base.info

THT direct: 0845 12 21 200 (Mon-Fri 10am-10pm; Sat/Sun 12noon-6pm) www.tht.org

* Ref:http://www.hiv-druginteractions.org/new/Uploaded_Attachment/76_Flu_Chart_update.pdf

CONFERENCE REPORTS

5th IAS Conference on HIV Pathogenesis, Treatment and Prevention

19-23 July 2009, Cape Town

As we went to press with this issue of HTB just as this important conference was concluding, we only include a brief overview of some of the most important studies. Further coverage will be included in the next issue.

In this issue we include the following articles:

- Five-year survival rates of 87% without routine CD4 or laboratory monitoring in DART study demonstrate an important model for ARV access programmes
- Biomarkers associated with mortality: long-term follow up from SMART
- Update on Interleukin-2 clinical trials
- Influenza vaccine effective in HIV+ adults
- Reducing HIV transmission during breastfeeding
- Treating children previously exposed to single dose nevirapine

For the first time, web casts of several sessions are available via the conference website together with searchable online abstracts and PDF files of many or the posters or presentations:

http://www.ias2009.org

The abstract database from the meeting is online at the same site.

Five-year survival rates of 87% without routine CD4 or laboratory monitoring in DART study demonstrate an important model for ARV access programmes

Simon Collins, HIV i-Base

The most important study results presented at the 5th IAS conference were from the DART (Development of AntiRetrovial Treatment in Africa) trial. [1]

Sponsored by the UK's Medical Research Council and University College London, DART randomised over 3300 treatment-naive patients in Uganda and Zimbabwe to be managed by either routine three-monthly CD4 count and laboratory monitoring (LCM group), or by clinically driven monitoring (CDM). Laboratory monitoring was also performed for this group, but results were only given to the treating doctor when a grade-4 toxicity was identified. Viral load was not monitored in either arm.

Criteria for switching patients to second-line therapy included a CD4 count less than 100 cells/mm3 in the LCM group or by symptoms/progression in the CDM group.

Patients were also randomised to one of three treatments, all with background AZT+3TC: abacavir (9%, n=300), nevirapine (7%, n=247) or tenofovir (74%, n=2469). d4T was not included as a first-line regimen, even though some patients switched to d4T during the study (for example to avoid anaemia). They were then followed for five years (median 4.9 years, IQR 4.5 – 5.3).

The Data and Safety Monitoring Board (DSMB) closed an earlier component of DART looking into treatment interruptions in March 2006.

The rationale behind DART was to determine whether ARVs could be used effectively without routine monitoring, in order to broaden access to treatment in settings where CD4 and laboratory monitoring are either no available or where they are difficult to access.

Enrollment criteria included being treatment-naive with a CD4 count <200 cells/mm3. Baseline median CD4 count and mean viral load were 86 cells/mm3 (IQR 31-139, range 0-199; one-third of patients had a CD4 count <50 cells/mm3) and 5.4 log (SD $\pm$0.7) copies/mL. WHO stage 2/3/4 was diagnosed in 20%, 56% and 23% patients respectively.

At the conference DART had a separate satellite symposium within the main conference programme and this is one of the sessions that has been web cast. The top line results were both impressive and challenged common assumptions. Both arms showed a remarkable and similar 5-year survival rate - 90% vs. 87% in the lab and clinical arms respectively - separated only by a small percentage difference that only occurred after the first two years on study. This compared to an historical 5-year survival rate prior to HAART of only 8%. Clinic attendence was >98% with high reported adherence and only 7% patients lost to follow-up over five years.

The event rates for a new WHO Stage 4 event or death were 6.94 versus 5.24 per 100 person-years in the CDM vs. LCM arm [n=459 (28%) vs. 356 (22%) HR 1.31 [1.14-1.51], log-rank p=0.0001]. Death rates/100PY were 2.94 in CDM versus 2.18 in LCM (p=0.004). Differences between strategies occurred from the third year on ART whereas lower rates of switching to second-line ART occurred in CDM from the second year. There were no differences between strategies in time to first serious adverse event, grade-4 toxicity or ART-modifying toxicity (see Table 1).

Table 1: 5-year event results from DART study

	Event rate/100 PY		HR [95%CI] p-value
	CDM	LCM	
New WHO Stage 4 event or death	6.94 n=459 (28%)	5.24 n=356 (22%)	HR 1.31 [1.14-1.51] log-rank p=0.0001
Death	2.94	2.18	p=0.004
Time to first SAE			HR 1.12 [0.94-1.31] p=0.20
Time to grade-4 toxicity			HR 1.08 [0.97-1.20] p=0.18
Time to ART-modifying toxicity			HR 1.01 [0.88-1.16] p=0.85

Around 60% of patients in each arm remained on their first line therapy after five years, with 20% modifying one or more drugs for tolerability and 20% of patients in each arm switching to second-line.

The higher mortality in the clinical monitoring arm was explained by patients being switched to second-line treatment at lower CD4 counts than the laboratory monitored group.

In an analysis of the two strategies, 3-monthly routine monitoring was determined to not be cost effective (based on the cost of treatment used in DART and relative to the WHO target for Incremental Cost Effectiveness Ratio (ICER) of 3 x GDP per capita). [2]

Lab unit costs were CD4 ($8.80), haematology ($5.30) and biochemistry ($29.50), with biochemistry carrying the highest cost with the least efficacy benefit. This was used to support the DART main conclusion that treatment shold not be witheld while waiting for monitoring and that resources for treatment access programmes should prioritise treatment over monitoring.

Several other presentations at the IAS conference presented a wealth of other aspects of the study including:

- Impact of different WHO 3/4 events on ART on subsequent survival (Abstract MOPEB003)
- Impact of cotrimoxazole in patients on ART: showing a 50% reduction in mortality during the first 72 weeks independent of CD4 count (Abstract MOPEB020)
- 5 year follow-up of participants initiating ART with Combivir plus nevirapine or abacavir (randomised): showing >90% survival and >80% alive and event-free, with clear virological and CD4 advantages for the nevirapine arm (Abstract MOPEB057)
- Assigning clinical endpoints in clinical trials in resource limited settings (Abstract TUPEB098)
- Impact of ART on incidence of malaria in Uganda (Abstract TUPDB104)
- 5 year follow-up of creatinine and estimated GFR in patients receiving and not receiving TDF first-line: showing overall low incidence of renal impairment on all regimens (2.9% GFR ever <30, 5.9% confirmed <60) with no differences between the LCM and CDM arms (Abstract TUPEB184)
- Pregnancy outcomes in women in DART: showing 378 pregnancies (57% live births, 6% still births and 36% termination/ miscarriage), similar rate of congenital abnormalities (~3%) as the ARV pregnancy register, and no HIV-infected babies to date (Abstract WEPEB261)

These and other presentations are now posted on the MRC website. [3]

See the next issue of HTB for detailed coverage of some of these studies.

C O M M E N T

These results strongly support expanding access to treatment to wider populations independent of access to routine laboratory monitoring and that delaying treatment access while waiting for laboratory infrastructure to be developed is resulting in extensive mortality and morbidity.

While the cost effectiveness analysis was limited to the strategy determined at the study outset, a sensitivity analysis looking at absolute real world costs based on using generic drugs (rather than subsided Western brands) and using an annual CD4 count from year two would be likely to bring this within the WHO target, and may reverse the slightly higher mortality linked to late CD4 switching seen in the clinical monitoring arm.

For example, in DART the annual drug costs for the three first line treatment arms were $432 (tenofovir), $444 (nevirapine) and $698 (abacavir) and $954 for second-line (lopinvir/r + ddl).

The modelling for the DART analysis concluded that CD4 tests would have to drop to $3.80 or less to be cost-effective, but this was based on providing 4 tests per year. Simply adding an annual test after two years would raise the minimum target cost per CD4 test to $15.20, which is well over the current costs. This implies that an annual CD4 test is actually cost effective and would detect those patients with CD4 counts <100 cells/mm3 who are at highest risk of serious events.

It is important to note that DART did not recommend excluding laboratory monitoring: the strategy was for treating without routine three-monthly monitoring, and the difference is critical to the study interpretation.

These results should also not be used to reduce the research and investment into the development of low cost diagnostics.

References:

1. Mugyenyi P et al. Impact of routine laboratory monitoring over 5 years after antiretroviral therapy (ART) initiation on clinical disease progression of HIV-infected African adults: the DART Trial final results. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 19-22 July 2009, Cape Town. Oral abstract TUSS102.
   http://www.ias2009.org/pag/Abstracts.aspx?AID=3807
2. Gilks C et al. Cost effectiveness analysis of routine laboratory or clinically driven strategies - DART trial. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 19-22 July 2009, Cape Town. Oral abstract TUSS103.
   http://www.ias2009.org/pag/Abstracts.aspx?AID=3830
3. DART study home page, MRC.
   http://www.ctu.mrc.ac.uk/dart

Biomarkers associated with mortality: long-term follow up from SMART

Nathan Geffen, i-Base and TAC

A poster at IAS2009 by Nick Paton and the INSIGHT SMART Study Group presented long-term follow-up data from the SMART study on biomarkers associated with mortality. [1] This analysis extended an earlier nested case-controlled study of the association between biomarkers and mortality.

The earlier study identified all 85 patients who had died up to 11 January 2006, ie the date that enrollment into SMART was stopped. Each death was matched to two controls by country, age, gender and randomisation date. The study evaluated four inflammatory markers, hsCRP (C-reactive protein measured using the highly sensitive test), interleukin-6 (IL-6), Serum amyloid A and serum amyloid P. It also examined three coagulation markers, D-dimer, PA1-1 and Prothombin fragment 1+2 (F1.2). Three markers, hs-CRP, IL-6 and D-dimer, were found to have a statistically significant association with mortality on both adjusted and unadjusted odd ratios.

Table 1: Case-controlled odd ratios by baseline biomarker levels

Marker	Unadj. OR (4th /1st quartile)	P-value	Adj. OR (4th/ 1st quartile)	P-value
CRP	2.0	0.05	2.8	0.03
IL-6	8.3	<0.0001	11.8	<0.0001
D-dimer	12.4	<0.0001	26.5	<0.0001

The extended analysis reported at IAS2009 included all deaths up to 11 July 2007 in order to determine whether the association between these biomarkers and mortality persists. There were 167 deaths in the SMART cohort up to that point, 85 before the protocol modification (to offer all patients continuous treatment) and 82 post-modification. For this analysis, the deaths were however divided into early (<=2 years after randomisation, n = 95) or late (>2 years, n = 71). Two cases were matched to each death as in the baseline study. The baseline values of two of the three biomarkers (IL-6 and D-dimer) continued to be statistically significant predictors of late deaths and there was a trend for CRP to be a predictor of late deaths (see Table 2).

Table 2: Baseline biomarker levels and risk of death

Marker	Early (<2yrs) v. Late (>2yrs)	Deaths		Controls		Adj. OR *	p-value
		No.	Median	No.	Median		
Hs-CRP (ug/ml)	Early	96	3.13	188	2.08	2.8	0.009
	Late	71	3.09	137	1.93	2.8	0.08
IL-6 (pg/ml)	Early	92	3.58	184	2.14	5.9	<0.0001
	Late	67	3.72	133	2.33	6.4	0.004
D-dimer (ug/ml)	Early	94	0.45	188	0.24	7.3	<0.0001
	Late	69	0.31	138	0.24	8.3	0.002

* 4th/1st quartile

Greater predictors of risk than other factors

Table 3 shows some of the other risk factors for deaths that have been found in SMART (note that where p-values show non-significance, the factor can still be significant when the early and late groups are counted together).

Table 3: Risk factors associated with mortality in SMART

Risk factor		**Deaths (%)**	**Controls (%)**	**p**
Hepatitis B or C	Early	38.9	20.7	0.002
	Late	46.5	19.3	0.0001
Current smoker	Early	50.5	34.0	0.006
	Late	64.8	38.6	0.005
Diabetes	Early	18.9	10.6	0.07
	Late	22.5	13.6	0.08
Blood pressure drugs	Early	37.9	25.0	0.02
	Late	38.0	23.6	0.02
Prior CVD history	Early	10.5	5.9	0.01
	Late	15.5	2.1	0.002
Total/HDL cholesterol	Early	4.4	4.7	0.06
	Late	4.8	4.8	0.99
Treatment group (% on structured breaks)	Early	63.2	52.1	0.09
	Late	59.1	50.7	0.27

The authors noted that IL-6, hs-CRP and D-dimer are associated with greater risk of mortality than smoking and diabetes and about an equivalent risk of prior cardiovascular disease. They conclude that interventions to decrease inflammatory and coagulation pathway activation may be of long-term benefit for people with HIV.

C O M M E N T

The association between mortality and hs-CRP, IL-6 and D-dimer is significant, even after long-term follow-up and the termination of the structured treatment interruption arm. This highlights the importance of further research on whether anti-inflammatory medicines will have an additional role in HIV management of high-risk patients.

It would be interesting to know the association between these biomarkers and mortality is in the uninfected population. If they are similarly prognostic, then the question is how much of the associations seen in SMART are HIV-specific.

The role of early HAART in mitigating the association with mortality also needs to be determined.

References

1. Paton N. Association between activation of inflammatory and coagulation pathways and mortality during long-term follow up in SMART. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention. 19-22 July 2009, Cape Town. Oral abstract MOPEA034. http://www.ias2009.org/pag/Abstracts.aspx?AID=3388

Update on Interleukin-2 clinical trials

Nathan Geffen, i-Base and TAC

In the March/April 2009 issue we reported on the results of the SILCAAT and ESPRIT interleukin-2 (IL-2) trials. These trials found no clinical benefit from using IL-2 with ART. At IAS2009, Abdel Babiker presented a pooled data analysis of the two studies. [1]

In addition, Jorge Tavel presented the findings of the STALWART IL-2 trial, which was unblinded early following the negative results of the SILCAAT and ESPRIT trials. [2]

In the combined ESPRIT and SILCAAT analysis, 2,920 patients were randomised to ART plus IL-2 and 2,886 took ART without IL-2. There were 39,902 person-years, 550 primary events and 381 deaths. The pooled analysis showed no statistically significant differences in opportunistic disease or death between ART + IL-2 compared to ART alone (HR=0.93; 95%CI: 0.78-1.09; p=0.33). For opportunistic diseases alone, HR=0.88 (95%CI: 0.68-1.13; p=0.32). For all cause mortality alone, HR=0.96 (95%CI: 0.78-1.17; p=0.68). There were however significantly more adverse events in the IL-2 arms (HR=1.19; 95%CI: 1.06-1.33;p=0.002).

Babiker explained that this suggests that cells induced by IL-2 have no role in host defense or that the negative effects of IL-2 neutralised any improvements in host defense conferred by IL-2.

The STALWART trial had three arms, IL-2 alone (IL-2; n=89), IL-2 with short-course ART at the time of IL-2 cycles (IL-2+; n=87) and a control group that using neither IL-2 nor ART (n=91). The cycled ART regimen involved 14 days of ART preceding the first IL-2 cycle (which lasted five days) followed by two days of ART. This was the same in subsequent IL-2 cycles, except the pre-IL-2 ART regimen was shortened to three days.

As with ESPRIT and SILCAAT, there was a significant rise in CD4 counts for people on both IL-2 arms (+114 on IL-2; +110 on IL-2+; -21.8 in the control; p<0.001 for both arms compared to control). A greater number of patients assigned to the control subsequently started ART.

Both IL-2 groups were associated with a significantly greater number of grade 3 or 4 adverse events. Five patients in each of the IL-2 groups experienced an opportunistic disease or died versus one patient in the control. People in the IL-2 groups started continuous ART less frequently probably because of their IL-2 elevated CD4 counts.

C O M M E N T

These results confirm the lack of clinical benefit from IL-2 in the setting of HAART, and no apparent functional advantage from IL-2-induced increases in CD4 count.

CD4 counts in patients who have used IL-2 may therefore be artificially high, and HAART should perhaps be started in these patients at higher CD4 counts than recommended in treatment guidelines.

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Influenza vaccine effective in HIV-positive adults

Nathan Geffen, i-Base and TAC

A poster at IAS 2009 by Madhi and colleagues reported the results of a double-blind, randomised, placebo-controlled trial to examine the efficacy of influenza vaccines in HIV-positive adults. Specifically, the study tested the seasonal trivalent subunit vaccine, which protects against three H1N1 and H3N2 influenza strains, two of which were isolated in 2006 and one in 2007. [1]

This was the first community-based randomised controlled trial of the trivalent subunit influenza vaccination in HIV-positive adults. A previous randomised controlled trial in the US on HIV-positive out-patients at a military health facility found that 10/47 patients who received placebo acquired laboratory confirmed influenza versus 0/55 patients who received this type of vaccine (p<0.001). [2]

A Cochrane Review of the vaccine in healthy adults has found this type of vaccine to be 30% effective (95%CI 17%-41%) against influenza-like illness, and 80% (95% CI 56% to 91%) effective against influenza when the vaccine matched the circulating strain and circulation was high, but decreased to 50% (95%CI 27%-65%) when it did not match the circulating strains. [3]

Participants were vaccinated prior to the 2008 influenza season in South Africa. Oropharyngeal swabs were taken from patients with influenza-like symptoms or respiratory illness. Culture and PCR tests were used to identify influenza strains. Only events 14 days post-vaccination were compared.

The number of HIV-positive people enrolled was 506. Of these, 101 were ART-naive (52 received vaccine, 49 received placebo) and 405 were on ART (203 received vaccine, 202 received placebo). Median age was 36. Female to male ratio was 5 to 1 in the vaccine arm and 6 to 1 in the placebo one. Median CD4 was 372 (IQR: 254-489) and 363 (IQR: 252-517) in the two arms respectively. Nine women were pregnant in the vaccine arm and four in the placebo one.

Over 90% of patients on HAART were virally suppressed in both arms. The median time on HAART at the time of randomisation was 23 months.

The percentage of people who developed influenza on the placebo arm was 5.3% using a passive surveillance method. [4] The rate of influenza illness was 0.06 per 100 person weeks in the vaccine arm and 0.25 per 100 person weeks in the placebo one. The vaccine efficacy was 75.4% (95%CI 14-93). The protective effect against the seasonal H1N1 strain was 73.5% (95%CI 4-93). There was one case of influenza B and no cases of H3N2 or untyped A.

The authors concluded that their findings support the use of the trivalent subunit influenza vaccine in HIV-positive adults.

C O M M E N T

This study supports vaccinating HIV-positive adults against seasonal influenza, as is routinely recommended in the UK. Because the vaccine is developed seasonally, its efficacy will change from year to year. The seasonal vaccine does not provide protection against the current H1N1 strain of swine flu.

At present there is no data on the effect influenza vaccines would have on reducing mortality in HIV-positive people as the contribution of HIV to influenza mortality is not well understood. Nevertheless, it is plausible that the reduced influenza cases conferred by the vaccine will reduce mortality as well.

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Reducing HIV transmission during breastfeeding

Polly Clayden, HIV i-Base

Introduction

Three late breaker posters showed data from randomised trials evaluating different maternal and infant ARV regimens, among women not indicated to receive HAART by current guidelines, in order to reduce the risk of mother to child transmission, particularly during breastfeeding. [1, 2, 3]

Mma Bana

In an oral presentation, Roger Shapiro from Harvard University, Boston, presented findings from the Mma Bana Study. Mma Bana is a randomised controlled trial, conducted in Botswana, comparing antiretroviral regimens in pregnant and breastfeeding HIV-positive women. [1]

This study enrolled 730 women from four clinical sites. Women were stratified by CD4 count. Those who did not meet the eligibility criteria for HAART, with CD4 $\geq$200 cells/mm3 were randomised to receive: abacavir (ABC), zidovudine (AZT) and lamivudine (3TC) co-formulated as Trizivir (Arm A), or lopinavir/ritonavir (LPV/r), AZT and 3TC as Kaletra and Combivir (Arm B). Women with CD4 counts <200 cells/mm3 were enrolled into an observational arm and received nevirapine (NVP) plus AZT and 3TC in accordance with Botswana National Guidelines.

Women with higher CD4 counts (n=560) were randomised between 26-34 weeks of gestation to Arm A or Arm B and they continued treatment until weaning their infants within 6 months. Women in the observational arm (n=170) initiated treatment at 18-34 months and continued indefinitely. This group also weaned their infants before 6 months.

All women received supplementary AZT during delivery. Infants received a single dose of NVP and one month AZT post partum. Follow up will continue for two years post partum.

The primary endpoints of the study were viral load <400 copies/mL at delivery and throughout breastfeeding and overall rate of mother to child transmission (MTCT).

Dr Shapiro reported low loss to follow up with 95% of mothers and 97% of mothers followed to 6 months or death. The majority of participants met both virologic and transmission endpoints: 99% women had viral load <400 copies/mL at delivery and 99.7% during breastfeeding; and 99.6% infants had birth PCR results (3 died before test) and 95% at 6 months or within one day of testing.

Baseline characteristics of the women were similar in the two randomised arms, their median ages were 26 and 25 years, CD4 393 and 403 cells /mm3 and viral load 13,300 and 9,100 copies/mL in Arm A (n=285) and Arm B (n=275) respectively. Both randomised arms had a median baseline gestational age of 27 weeks. Women in the observational arm (n=170) were older, median 29 years, with lower CD4 counts, 147 cells/mm3 and higher viral loads, 51,700 copies/mL. Women received a median of 11 weeks in the randomised arms and 13 weeks in the observational arm of HAART prior to delivery.

Adherence to breastfeeding and HAART was good, 97% of women initiated breastfeeding and 93% breastfed exclusively until weaning. The majority of women, 71%, breastfed for >=5months and only 1% breastfed beyond 6 months. HAART adherence was similar across all three arms, 6% of women missed >= 3 days treatment.

At delivery (n=709), 96%, 93% and 94% of women in Arms A, B and the observational arm respectively had viral load <400 copies/mL (A vs. B, 95% CI for difference, -2%, 10%). During breastfeeding (n=669), 92%, 93% and 95% had viral load <400 copies/mL (A vs. B, 95% CI for difference, -8%, 6%). Risk factors for detectable viral load were higher viral load at baseline, p<0.001 and later gestational age at enrolment, p<0.001.

At 6 months the overall transmission rate in this study was 1% (95% CI, 0.5%, 2.0%). Of these, 5 occurred in utero, there were no intrapartum transmissions and two were during breastfeeding (see Table 1: MTCT at 6 months in Mma Bana).

Table 1: MTCT at 6 months in Mma Bana

Infections, live born infants	Arm A ABC/AZT/3TC n=283	Arm B LPV/r/AZT/3TC n=270	Obs Arm NVP/ AZT/3TC n=156
In utero	3 (1.1%)	1 (0.4%)	1 (0.6%)
Intrapartum	0	0	0
Breastfeeding	2 (0.71%)	0	0
Total	5 (1.8%)	1 (0.41)	1 (0.6%)

There was no statistically significant difference between Arms A vs. Arm B, p=0.53. Dr Shapiro noted that these results excluded one unconfirmed HIV-infected infant that died in Arm A. When this infant was included in the analysis the difference did not reach statistical significance, p=0.42.

Maternal risk factors for transmission at delivery were fewer weeks of HAART, higher baseline viral load and poorer adherence. Higher baseline viral load and poorer adherence were also risk factors for transmission during breastfeeding.

Stillbirth occurred more frequently in the observational arm: 11 (7%) vs. 8 (3%) and 5 (2%) in Arms A and B, randomised vs. observational, p=0.07. Prematurity was more frequent in Arm B vs. Arm A, 61 (23%) and 42 (15%) respectively, A vs. B, p=0.04, and in 16 (10%) in the observational arm. Low birth weight did not differ by HAART regimen, 37 (13%), 45 (11%) and 23 (15%) in Arms A, B and observational respectively. Nor was there a difference in congenital abnormality, which occurred in 5 infants in each arm (2%, 2% and 3% respectively).

There were few maternal deaths, 1 (<1%) in Arm A and 3 (2%) in the observational arm. Grade 3 or 4 maternal adverse events occurred in 42 (15%), 32 (12%) and 48 (28%) women in Arm A , Arm B and the observational arm respectively. These were treatment-limiting in 7 (2%), 6 (2%), and 18 (11%) women in Arms A, B and observational.

Dr Shapiro concluded that using maternal HAART, among 709 live births, the overall mother to child transmission rate was only 1% with only 2 (0.3%) of infections occurring during the 6-month period of breastfeeding. “The lowest MTCT rate ever recorded in a breastfeeding population”, he said.

BAN

In second oral late breaker, Charles Chasela from the University of Northern California Project, Lilongwe, Malawi showed preliminary, 28 week, results from the Breastfeeding Antiretroviral and Nutrition (BAN) study. [2]

Formula feeding is not recommended in Malawi due to its high cost and greater association with infant mortality frequently observed in resource- limited settings.

BAN is a randomised controlled trial of mother infant pairs. Its aim is to evaluate two antiretroviral interventions over 24 weeks of exclusive breastfeeding followed by a four-week period of weaning, among women with CD4 counts >250 cells/mm3 with infants uninfected at birth and ≥2000 grams.

In this study all mothers and infants received single dose NVP plus one week AZT/3TC “tail” coverage. All women received nutritional supplementation, which the investigators described as, “enhanced standard of care”. Mother and infants were randomised to receive maternal HAART or NVP infant prophylaxis or nutritional supplementation alone (control). After cessation of breastfeeding, infants

receive plumpy nut weaning food until 48 weeks. The primary endpoint was infant HIV status at 28 weeks.

A total of 2367 mother infant pairs were randomised within one week of birth; 851 received maternal HAART, 848 received infant NVP and 668 were in the control arm. There were no significant differences in the participants across the arms. The women's median ages were 26, 25 and 26 years in the HAART, NVP and control arms respectively, p=0.7. Their median CD4 counts were 428, 440 and 442 cells/mm3, p=0.16.

Dr Chasela noted that during the trial the maternal HAART changed from a NVP-based regimen to nelfinavir in February 2005 and to LPV/r in January 2006. Nucleosides were AZT and 3TC.

There were no significant differences in maternal grade 3/4 toxicities except for low neutrophil count in women receiving HAART, 6.7% vs. 2.9 and 2% in the HAART, NVP and control arms, p<0.0001. This is known to be associated with AZT.

Among the infants, 16/848 experienced possible NVP hypersensitivity which all resolved when the NVP was discontinued. Additionally symptoms were observed in one infant whose mother was receiving NVP.

The investigators found both the infant NVP and maternal HAART regimens significantly reduced 28 week HIV transmission to the infants compared with the enhanced control arm.

The 28-week transmission in the infant NVP arm was 1.8% vs. 6.4% in the control arm, p< 0.0001. In the maternal HAART arm the transmission rate was 3.0% vs. 6.4% in the control arm, p=0.0032.

The estimated HIV-transmission or infant death rate was 7.6% in the control arm vs. 4.7% in the maternal HAART arm, p=0.031. This estimation was 2.9% vs. 7.6% in the NVP and control arms, p>0.0001.

Dr Chasela concluded that this study shows both maternal and infant ARV prophylaxis during 28 weeks of breastfeeding are safe and effective in reducing postnatal mother-to-child transmission of HIV.

He added, "Although this study was not powered to directly compare the maternal and infant interventions, there was some suggestion that the transmission of HIV was lower in the Infant NVP arm."

Final 28-week visit for this study will be August of this year and 48-week visit will be January 2010.

Kesho Bora

And a late breaker poster authored by Isabelle de Vincenzi and the Kesho Bora Study Group reported preliminary data from a comparison of maternal HAART to short course prophylaxis regimens in women also not currently eligible for treatment.

In this study - conducted in five sites in Burkina Faso, Kenya and South Africa - pregnant women with CD4 counts 200-500 cells/mm3 were randomised between 28 and 36 weeks gestation to receive either maternal HAART (AZT+3TC+LPV/r to approximately 6.5 months after delivery or breastfeeding cessation if earlier) or short- course AZT plus single-dose NVP in labour. All infants received single-dose NVP post partum. During the course of the study one-week maternal "tail" coverage was added to the short course regimen and one week AZT for all infants.

Participating women received infant feeding counselling recommending either replacement feeding with free formula or exclusive breastfeeding, weaning from 5.5 months over a two-week period.

Women in both study arms were a median age of 27.4 and had a median CD4 count of 335 cells/mm3 at enrollment.

There were 805 live births, 402 in the HAART and 403 in the short course arms.

The investigators reported 76.4% and 78.2% of infants were ever breastfed in the HAART and short course arms respectively. Of these 47.5% and 45.6% were breastfed exclusively and the median duration was 21.4 weeks.

Kaplan-Meir estimates of the culmulative infant infection rates in the HAART arm were: 1.8% (95% CI, 0.8-3.7) at birth, 3.3% (95% CI, 1.9-5.6) at 6 weeks, 4.9 (95% CI, 3.1-7.5) at 6 months and 5.5 (95% CI, 3.6-8.4) at 12 months.

In the short course arm these rates were: 2.2% (95% CI, 1.2-4.3) at birth, 4.8% (95% CI, 3.1-7.4) at 6 weeks, 8.5 (95% CI, 6.1-11.8) at 6 months and 9.5 (95% CI, 6.9-13.0) at 12 months. This gave a 42% reduction in transmission risk at 12 months, p=0.039.

Provisional estimate of cumulative death rate at 12 months showed 6.3% (95% CI, 4.3-9.3) in the HAART arm vs. 10.0% (95% CI, 7.3-13.6) in the short course arm. This was a risk reduction of 37% but this was not significant, p=0.086.

And provisional estimate of HIV infection or death at 12 months showed 10.4% (95% CI, 7.7-13.9) in the HAART arm vs. 16.3% (95% CI, 12.9-20.5). Giving a 36% risk reduction, p=0.022.

Subgroup analysis of infants who ever breastfed revealed a cumulative infection rate of 5.0% vs. 8.8% at 6 months and 5.9% vs. 10.2% at 12 months, in the HAART vs. short course arms. This was not significant, p=0.064.

Cumulative infection rate for infants whose mothers had a baseline CD4 200-350 cells/mm3 was 5.5% vs. 10.5% at 6 month and 6.1% vs. 11.1% at 12 months in the HAART and short course arms, p=0.044.

Among infants whose mothers had a baseline CD4 350-500 cells/mm3 the rates were 4.1% vs. 5.9% at 6 months and 4.9% vs. 7.4% at 12 months, which were not significant, p=0.33.

The investigators concluded that maternal HAART given to women with CD4 counts 200-500 cells/mm3 during pregnancy and

through breastfeeding reduces risk of HIV transmission and improves HIV- free survival compared to standard short course regimen. They noted that the largest effects were between 6 weeks and 6 months and among infants with mothers with baseline CD4 200-350 cells/mm3.

Importantly they found some postnatal HIV transmissions occurred despite maternal HAART and suggest that mothers may not have been able to wean at 6 months, underlining the importance of continuing HAART until complete breastfeeding cessation, or that this may be explained by inadequate adherence.

Final 12 months results from this study will be available in December 2009 and 18 months results in June 20010. These will include data on maternal health.

C O M M E N T

Together these data contribute to what we know and will influence policy and clinical practice. However, they do not yet resolve the question of how best to prevent mother to child transmission among women not yet indicated for treatment for their own health during pregnancy and breastfeeding.

It is difficult to compare transmission rates between these studies, as there are differences to consider between duration of antepartum treatment, maternal baseline CD4, exclusive vs. mixed breastfeeding, and levels of adherence, etc.

Mma Bana reported 93% exclusive breastfeeding, over 90% adherence and nearly three months antepartum treatment, all of which combine to give lower transmission rates than the other studies. This does not tell us though whether HAART is better than short course plus infant prophylaxis for women with high CD4 count. In Kesho Bora, for the subgroup of women with CD4 350-500 cells/mm3, there was no difference with HAART vs. short course and no postnatal prophylaxis.

Kesho Bora looked at two issues: transmission rates at birth, and postnatal transmission rates. Transmission at birth reflects receipt of HAART vs. short course during pregnancy and here transmission rates were almost identical. Postnatal transmission rates after birth reflect a comparison of HAART vs. nothing during breastfeeding. HAART was better than nothing. HAART is better than short course with nothing during breastfeeding. We already know infant prophylaxis is better than nothing, so that question is no longer relevant. The important question for breastfeeding is: maternal HAART vs. infant prophylaxis. The BAN study showed both work and, in this study, if anything, infant prophylaxis had the lower postnatal transmission rate.

But for maternal HAART to be most effective, starting at birth (as in BAN) is not an ideal intervention, it takes weeks, even months, for someone to be fully suppressed with HAART so starting too late in pregnancy (or at delivery) will put the baby at risk while the virus is detectable (though the threshold viral load for quantifying risk is not clear). In Mma Bana, the investigators found starting HAART >30 weeks gestation led to only 85% suppression by delivery whereas starting <30 weeks was associated with 97% suppression at delivery. This may be associated with early breastfeeding risk as well as in utero/intrapartum risk (previous studies correlate breast milk viral load with transmission risk and plasma and breastmilk viral load are also correlated).

In Kesho Bora there was less exclusive breastfeeding and possible poorer aherence and the rate of viral suppression was not presented (but should be soon). Their median time on HAART before delivery was shorter than Mma Bana so it is likely that more women were unsuppressed at delivery and in early breastfeeding. Concerns about mixed feeding in later breastfeeding are probably less important than those of suppression and adherence. If there is little or no virus in breast milk then that would most likely prevent additional risk from gut issues related to mixed feeding, but the relative contribution of different transmission risks have not yet been studied.

It was interesting to see data for a triple nucleoside regimen in Mma Bana for women with higher CD4 counts, but it is likely that lopinavir/r-based regimens will remain the standard of care for women in this situation particularly as it more available and cheaper in Africa and has more safety data. Importantly both regimens performed very well in this study.

None of these studies looked at breastfeeding beyond 6 months post partum, which could contribute to better infant survival but also to more potential risk for failure over longer duration and greater cost.

So we still need data to answer questions concerning the efficacy and optimal duration of maternal HAART vs. infant prophylaxis for preventing post-natal mother to child transmission. And we need more information about the safety of stopping (or continuing) maternal HAART if used just to prevent mother to child transmission in healthier women. PROMISE, a multi-country study beginning soon will look at these questions in 8,000 women who do not need treatment for their own health (<350 cell/mm3).

Our next issue of HTB will include our full report on maternal/infant health and mother to child transmission from IAS 2009.

Thanks to several researchers, particularly Roger Shapiro and Lynne Mofenson, for discussion of these studies.

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Treating children previously exposed to single dose nevirapine

Polly Clayden, HIV i-Base

Two studies presented at the 1st International Workshop on HIV Pediatrics, 17-18 July 2009, Cape Town, South Africa and 5th IAS Conference on HIV Pathogenesis Treatment and prevention 19-22 July 2009 looked at strategies for treatment of HIV-infected children with prior exposure to nevirapine (NVP) to prevent mother to child transmission.

IMPAACT P1060

In an oral presentation at the paediatric workshop, Avy Violari from the University of Witwatersrand, Johannesburg, South Africa, presented preliminary findings from the IMPAACT P1060 trial. [1] These data were also shown at the 5th IAS Conference as a late breaker poster. [2]

IMPAACT 1060 was a randomised trial conducted at 10 sites in 7 African countries. In this trial, two groups of HIV-infected children age 6 months to 3 years and eligible for treatment according to WHO criteria: Cohort 1, exposed (n=288) and Cohort 2, unexposed (n=288) to single dose NVP, were randomised to receive either lopinavir/r or NVP plus zidovudine (AZT) and lamivudine (3TC), with 144 children in each treatment group.

Children were stratified by age <12months vs. >=12 months with equal number to be enrolled in each age group.

The primary endpoint was virologic failure (defined as <1 log decrease in viral load between weeks 12 -24 or >400 copies/mL at week 24), treatment discontinuation or death by week 24.

The investigators used Kaplan-Meier curves to estimate failure rates at week 24. Differences between treatment arms were weighted by the inverse of the variance in each age group.

A similar study of mothers exposed and unexposed to single dose NVP had also been conducted (A5208). In this trial – which we reported in previous issues of HTB – the arm in which exposed mothers received NVP-containing HAART was stopped early by the Data Safety Monitoring Board (DSMB) due to superior performance of the LPV/r- containing HAART arm. [3, 4]

Dr Violari reported that following a scheduled DSMB review of IMPAACT 1060 on 20 April 2009, enrolment to Cohort 1 had also closed prematurely due to a trend towards consistency with the A5208 results. Children in Cohort 1 were evaluated and discussions with their parents or guardians were held to decide whether to switch children receiving NVP to LPV/r. Cohort 2 is to continue enrolment and study as planned.

At the time of the DSMB review, Cohort I had enrolled 153/288 children with a median follow up of 48 weeks. The median baseline age of the children was 0.7 years (75% <12 months), median CD4 percentage 19%, and median viral load >750,000 copies/mL. Results at week 24 by primary endpoints are detailed in Table 1.

Table 1: Cohort 1, week 24 primary endpoints (from Kaplan- Meier curve)

Age months	NVP (n)	Failure %	LPV/r	Failure %	NVP-LPV/r
<12	60	45%	63	23%	22%
>=12	22	29%	19	17%	11%
All	82	39%	82	22%	18%

Difference in week 24 failure rate (NVP-LPV/r): all 18% (95% CI 2%-33%), p=0.015.

Of 115 children tested, 16 (14%) had baseline NVP resistance, mostly Y181C (n=14). The investigators found the difference in viral failure between arms was greater among the 16 children with baseline resistance (57%) compared to the 99 without resistance (17%).

The investigators suggested these data emphasise the need for better prevention of mother to child transmission strategies including post partum “tail” coverage and maternal HAART. And that prioritisation of resources for mother-infant pairs should be encouraged.

NEVEREST

Several guidelines already recommend using LPV/r-based treatment for single dose NVP-exposed infants.

Louise Kuhn from Colombia University, New York, USA and Ashraf Coovadia from the University of the Witswatersrand, Johannesburg, South Africa, presented findings from the NEVEREST study. NEVEREST is an investigation to see if NVP-exposed children, initially suppressed on LPV/r-based HAART can safely switch to a NVP based regimen.

In this study children 6 weeks to 2 years of age and eligible for treatment (n=323), were initiated on LPV/r plus 3TC and d4T. After achieving a viral load <400 copies/mL and maintaining it for >= 3months, children were randomised (n=195) to either remain on LPV/r (control, n=99) or switch to NVP (switch, n=96), and then followed to 52 weeks post randomisation.

Baseline (pre-treatment) characteristics of the randomised children were mostly similar: median age, 11 months vs. 9 months; median CD4 percentage 19.0% vs. 18.4%; and 57% vs. 54% had a viral load >750,000 copies/mL in the control and switch groups respectively. There was a larger group of younger children age 1-12 months in the switch group, 57.6% vs. 68.8%, but this difference was not significant.

At randomisation the median age of the children were 20 months vs. 19 months; median CD4 percentage 28.9% vs. 28.5% and 61% vs. 66% had a viral load <50 copies/mL in the control and switch groups respectively. The median time on LPV/r based therapy was 9 months in both groups.

Two children in each group died; 3 children in the control and 5 in the switch group were lost to follow up and 3 children in the control and 5 in the switch group started TB treatment.

The investigators reported 80% vs. 86% of children were adherent to the study medication at 36 weeks post randomisation in the control and switch groups respectively.

When the investigators looked at viral load <50 copies/mL to 52 weeks they found 42.4% children in the control group and 56.2% in the switch group sustained viral suppression, p=0.01. But allowing for one elevated result (blip) the two groups were similar, 72.8% vs. 73.4% in the control and switch groups respectively.

They suggested that poorer adherence in the control group, due to the unpleasantness in taste of LPV/r syrup, may have led to more blipping and, in turn, unsustained viral suppression to 50 copies/mL during follow up.

In contrast, when they looked at sustained suppression to <1000 copies/mL, 98% vs. 80% of children in the control and switch groups achieved this, p=0.001.

An analysis of patterns of viral suppression after the children were randomised revealed that of the children >50 copies/mL**,** 56% in the control group had viral load between 50-1000 copies/mL and the remaining 2% more than 1000 copies/mL. In the switch group more children had viral load more than 1000 copies/mL 20%; but fewer, 24%, were between 50-1000 copies/mL.

In the switch group, viral suppression <50 copies/mL at randomisation was predictive of sustained viral suppression <1000 copies/mL through 52 weeks: 86.1% of children with viral load <50 copies/mL at randomisation sustained viral suppression <1000 copies/mL through 52 weeks vs. 63.5% with viral load 50-400 copies/mL at randomisation, p<0.001. Likewise, the presence of NNRTI mutations prior to treatment predicted sustained viral suppression after switch: 88% children with no mutations sustained viral load <1000 copies/mL through 52 weeks vs. 55.3% with mutations, p=0.007.

The median CD4 percentage at 24 weeks in the control group was 30.0% vs. 33.2% in the switch group, p<0.0001. In the control group 16.3% of children had a CD4 percentage decline of 10% vs. 3.2% in the switch group, p=0.004. Weight for age declined >1 z-score in 13.1% of children in the control group vs. 4.2% in the switch group, p=0.03.

The investigators wrote that this study provides proof of concept that re-use of NVP is possible under some circumstances for HIV-infected children exposed to NVP prophylaxis and should be further investigated. They note that the clinical significance of low-level viraemia in the control group needs further study. Switching may provide a promising option for children originally initiated on PI-based HAART to preserve second-line options. At this stage, switching requires close virological monitoring after the switch in order to be done safely.

C O M M E N T

The 1060 results are unsurprising and entirely consistent with the earlier maternal data. Baseline nevirapine resistance and younger age appear to be associated with the performance of the nevirapine arm.

NEVEREST was interesting and this strategy deserves further investigation. Another NEVEREST trial of efavirenz vs. lopinavir/r is planned in nevirapine-exposed children >3 years old.

Both studies underscore the limited treatment options that are available for children, particularly in resource limited settings.

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1. Violari A et al. Nevirapine vs. lopinavir-ritonavir- based antiretroviral therapy (ART) in single dose nevirapine (sdNVP)-exposed HIV infected infants: preliminary results from the IMPAACT P1060 trial. HIV Pediatrics, 17-18 July 2009, Cape Town. Abstract O_08.
2. Palumbo et al. Nevirapine (NVP) vs. lopinavir-ritonavir (LPV/r)- based antiretroviral therapy (ART) in single dose nevirapine (sdNVP)-exposed

HIV-infected infants: preliminary results from the IMPAACT P1060 trial. 5th IAS Conference on HIV Pathogenesis Treatment and prevention 19-22 July 2009, Cape Town. Abstract LBPEB12.
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5. Coovadia A et al. Randomized clinical trial of switching to NVP-based therapy for infected children exposed to nevirapine prophylaxis. HIV Pediatrics, 17-18 July 2009, Cape Town. Abstract O_09.
6. Coovadia A et al. Randomized clinical trial of switching to nevirapine-based therapy for infected children exposed to nevirapine prophylaxis. 5th IAS Conference on HIV Pathogenesis Treatment and prevention 19-22 July 2009, Cape Town. Abstract MOAB103.

CONFERENCE REPORTS

10th International Workshop on Clinical Pharmacology of HIV Therapy

15-17 April 2009, Amsterdam

Introduction

The following reports from this meeting have been largely compiled from the abstracts of these studies.

It is disappointing that the abstracts from the virology-education meetings are not published online, and that only a selection of presentations from the meeting are available at:

http://www.HIVpresentation.com

A useful summary report of the drug-interaction studies presented at the meeting is available on the Liverpool University website (in the April 2009 news archive):

http://www.hiv-druginteractions.org/new/Content.asp?ID=431&TDM=

Reports in this issue are:

- Monotherapy study may explain previous poor clinical results when abacavir and tenofovir are used in combination
- Interactions between ARVs and the antimalarials atovaquone and proguanil
- Four weeks lopinavir/r to cover functional monotherapy when stopping HAART
- Efavirenz-related studies: genetics, smoking and TDM
- Atazanavir: a suitable case for TDM?
- Raltegravir PK in blood plasma and the genital tract
- A CYP2B6 haplotype influences nevirapine plasma concentrations following a single dose to reduce mother to child transmission
- Population pharmacokinetic model of nevirapine maternal to infant transfer through breastfeeding
- Phenotypic and genotypic inhibitory quotients and virologic response in treatment experienced children
- Tenofovir pharmacokinetics in three tenofovir-containing regimens in children and adolescents
- Bioavailability of Thai generic lopinavir/ritonavir

Monotherapy study may explain previous poor clinical results when abacavir and tenofovir are used in combination

Simon Collins, HIV i-Base

Goicoechea and colleagues from San Diego presented a detailed analysis that might explain the previous poor performance of some antiretroviral regimens that contain both abacavir and tenofovir, especially as this group and others found no evidence of reduced intracellular levels of either carbonavir triphosphate or tenofovir diphosphate, the active metabolites of abacavir and tenofovir respectively.

This study randomised 21 HIV-positive treatment-naive patients to seven days monotherapy with either abacavir or tenofovir, followed by seven days dual therapy with both drugs. Following a 35-day washout, the study was repeated with patients switched to receive the alternative nuke as initial monotherapy.

Intracellular levels of endogenous purines (dGTP for abacavir and dATP for tenofovir) were also measured and the ratio to intracellular metabolites was compared to the slopes of viral decay during the mono- and dual-therapy periods.

As the rate of viral decay remained unchanged following addition of tenofovir to abacavir alone (-0.15 log/day vs. -0.16 log/day) the researchers concluded that this confirmed a lack of additive antiviral effect.

Median dGTP and dATP (fmol/million cells) both tended to increase during dual vs. monotherapy, though not to statistical significance (2798 vs. 4301, p=0.11 and 3293 vs. 4638, p=0.08).

However, when abacavir was added to tenofovir monotherapy, the dATP increase was significant during dual therapy (3238 vs. 4534, p=0.047).

No intracellular parameters or ratio was related to abacavir viral response during monotherapy, but during tenofovir monotherapy viral decline was weakly correlated with dATP levels (rho= -0.05, p=0.07) and in all patients during dual therapy there was a weak trend for higher dATP to negatively correlate with viral decline (rho=0.407, p=0.13). However, the ratio of tenofovir TP:dATP was significantly associated with viral decline (rho=-0.529, p=0.045).

C O M M E N T

These results provide insight into a previously unexplained clinically significant interaction. As study numbers were low it would be important to confirm these initial findings in a larger trial.

The median viral load in these patients was around 5log copies/mL and it is unclear whether two periods of two-week monotherapy resulted in the development of resistance that would limit future treatment.

These results may have clinical significance for patients currently using abacavir and tenofovir in the same combination.

Ref: Goicoechea M et al. Alterations in endogenous purines may explain a non-additive antiviral effect with co-administration of tenofovir disoproxil fumerate (TDF) and abacavir (ABC). 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam. Oral abstract O-08.

Interactions between ARVs and antimalarials atovaquone and proguanil

Simon Collins, HIV i-Base

Van Luin and colleagues from Nijmegen presented results showing significantly lower levels of the common antimalarials atovaquone and proguanil, commonly used together as prophylaxis, in HIV-positive patients on HAART compared to HIV-negative controls.

Seven-day PK results from HIV-positive patients already on established HAART including efavirenz (n=19), lopinavir/r (n=19) or atazanavir/r (n=19) were compared to levels in 20 HIV-negative volunteers following single-dose atovaquone/proguanil (250/150mg), administered with a fat standardised breakfast. Patients who were negative for CYP2C19 defective *2 and *3 alleles, the key enzyme for proguanil metabolism, were excluded from the proguanil comparisons.

PK parameters were significantly lower in HIV-positive patients (all p<0.05), and are detailed in Table 1. Efavirenz or lopinavir/r resulted in considerably reduced levels suggesting increased dosing may be required. Atazanavir/r considerably lowered proguanil compared to the HIV-negative group, but more modestly lowered atovaquone suggesting that this interaction may be managed with perfect adherence.

Table 1. Mean [range] atovaquone and proguanil levels

	HIV-negative	efavirenz	lopinavir/r	atazanavir/r
Atovaquone				
AUC 0-t (h*mg/L)	112.9 [43.3-250.1]	35.3 [12.5-91.8]	39.1 [6.3-137.0]	75.3 [22.6-146.6]
Cmax (mg/L)	2.0 [0.44-4.0]	1.2 [0.39-2.8]	1.3 [0.40-3.0]	1.1 [0.54-2.2]
Proguanil (in patients without CYP2C19* or -*3)				
AUC 0-t (h*mg/L)	1.3 [0.40-10.3]	0.55 [0.12-1.8]	0.42 [0.12-1.8]	0.34 [0.10-0.63]

All comparisons to HIV-negative values: p<0.05.

C O M M E N T

Sn important problem with this study is the use of HIV-negative controls compared to HIV-positive patients, so the differences may have been due to differences in PK of antimalarials in HIV-positive people. These are interesting data, but the results need confirmation and cannot be regarded as definitive.

Ref: Van Luin M et al. Drug interactions between atovaquone/proguanil and antiretroviral agents. 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam. Oral poster O-19.

Four weeks lopinavir/r to cover functional monotherapy when stopping HAART

Simon Collins, HIV i-Base

Taylor and colleagues from Birmingham Heartlands Hospital presented results from a pilot study that switched 20 patients to four weeks lopinavir/r monotherapy on day 0 of a planned treatment interruption. [1]

This protective strategy was designed to reduce the risk of resistance while drug levels dropped, as many regimens combine individual drugs with different plasma and intracellular half-lives, and is complicated in the case of NNRTIs by genetic polymorphisms related to higher exposure and slower clearance. This strategy was previously discussed in a paper in AIDS as probably the safest way to stop treatment. [2]

Twelve of the regimens in this study were judged likely to risk functional monotherapy: 8 for NNRTIs and 4 for tenofovir or FTC.

Viral suppression was maintained in most patients, thoughout the period of monotherapy (14/17 with results), and three patients with detectable viral load at baseline experienced significant viral declines on lopinavir/r.

Lopinavir levels remained above the minimum target of 1000ng/mL, except in two patients with suspected non-adherence and viral load rebounded by week 8 in all 12 patients who discontinued lopinavir/r at week 4

The importance of this approach was highlighed by 6/12 patients on 'unbalanced' regimens having residual drug concentrations of their initial ARVs more than one week after stopping those combinations.

References

1. Taylor S et al. Kaletra single agent therapy as a universal ART stopping strategy: the STOP 2 study. 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam. Poster abstract P-17.
2. Taylor S, Boffito M, Khoo S, Smit E, Back D. Stopping antiretroviral therapy. AIDS 2007; 21:1673-1682. (20 August 2007). doi: 10.1097/QAD.0b013e3281c61394.
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Efavirenz-related studies: genetics, smoking and TDM

Simon Collins, HIV i-Base

Several studies presented interesting results on the PK of efavirenz.

In an oral presentation reporting higher rates of antiretroviral switching by patients with pharmacogenetic markers (notably genotype changes in CYP2B6 G516T) associated with an increased risk of side effects, Colombo and colleagues from the Swiss HIV Cohort reported that patients were more likely to switch from efavirenz if they carried these alleles (42% vs. 27%). [1]

Bensemmane and colleagues from a multicentre French study reported on the routine use of therapeutic drug monitoring (TDM) to manage individual patients on efavirenz from 2002-2008. [2]

The target level, based on historical estimates was 1000-4000 ng/mL. Of the 2545 patients (33% women) prescribed efavirenz at 600mg once-daily, with at least one TDM result for Cmin, approximately 5% had levels below the limit of detection for the test (<10ng/mL) suggesting non-adherence. 12% patients had levels below the minimum target, 61% were in the target range and 22% had Cmin levels >4000 ng/mL.

Of the 549 patients with high levels, 41% (n=188) adjusted the efavirenz dose to one of four once-daily doses: 400mg, 300mg, 200mg or 100mg (groups 1 to 4, respectively).

Table 1. Median efavirenz levels in patients with Cmin >4000 ng/mL

	N	Baseline Cmin (ng/mL)	Cmin after adjustment (ng/mL
Group 1	129	5547	2701
Group 2	2	5194	1664
Group 3	54	9263	2480
Group 4	3	11028	2245

Although the poster abstract provided minimal details on the relationship between drug levels and toxicity, it reported that approximately that only 22% of patients making a dose adjustment continued to experience persistent side effects. As the study was unblinded patients who knew they had reduced their dose may have reported side effects differently.

A second poster by Fayet and colleagues from the Swiss Cohort Study reported results from a small prospective study using TDM to individualise efavirenz dosing in 15 patients on stable EFV-based HAART, with levels in the highest quartile. [3]

At baseline, median efavirenz Cmin was 8,409 ng/mL (IQR 6610-10,370). The five patients with levels between 75-95 percentile reduced the efavirenz dose to 400mg QD and then ten patients above the 95th percentile reduced to 200mg QD.

Following dose reductions, ten patients with results achieved the target of 25-75th percentile range (median 2,856, IQR 2192-3157 ng/mL). Three months after the dose adjustment, all patients remained above the minimum 1000ng/mL lower target level and maintained viral load <40 copies/mL.

Cortes and colleagues presented results from a prospective 215 patients (13 women) in Chile, looking at both drug levels and genetics (CYP2B6: 516G>T and 983 T>C; and contitutive androstane receptor (CAR) rs2307424 polymorphisms). [4]

In the group as a whole, mean (±SD) levels were 3100 ng/mL (±1600), in samples taken a mean 11.9 hours (±1.6) post-dose. Eleven patients (5%) had levels <1000 and 45 (21%) had levels >4000ng/mL. Alleles at CAR, 516G>T and 983 T>C were present in 49%, 35% and 0% respectively, and were related to drug concentations in multivariate analysis (see Table 1).

As reported in other studies, c516 polymorphisms were related to efavirenz exposure.

This is the first report of the impact of the associations with the contitutive androstane receptor and the group also reported statistically significant lower levels in smokers compared to non-smokers (2.81 vs. 3.32 mg/L, p-0.02).

Table 1. Efavirenz drug exposure (mg/L) in relation to genetic plymorphisms

	GG (n=90)	GT (n=87)	TT (n=30)	p
CYP2B6 516	2.21	3.13	5.23	p<0.0001

	CC (n=50)	CT (n=109)	TT (n=48)	p
CAR rs2307424	2.97	3.28	2.53	p=0.008

C O M M E N T

These posters show the potential for individualising dosing in patients who metabolise efavirenz more slowly (whether due to genetics, hepatitis coinfection etc) and who end up with levels higher than the upper limit of the recommended target range.

The association with smoking status has not previously been reported.

It is unclear if the study adjusted for weight differences and whether this would make a difference to the results. If there is an association with weight, then the association with smoking would be in the opposite direction (ie. smokers tend to weigh less, so levels may be higher rather than lower).

References

1. Colombo S et al. Association of pharmacogenetic markers with premature discontinuation of first-line ART. 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam. Oral poster O-03.
2. Bensemmane R et al. Six years of routine therapeutic drug monitoring of efavirenz (EFV) in HIV-infected patients. 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam. Poster abstract P-48.
3. Fayet A et al. Successful TDM-guided efavirenz dose reduction in virologically-controlled patients. 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam. Poster abstract P-47.
4. Cortes C et al. Correlates of efavirenz exposure in HIV infected patients from Chile reveals novel associations iwith a polymorphism in the contitutive androstane receptor and smoking. 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam. Poster abstract P-04.

Atazanavir: a suitable case for TDM?

Simon Collins, HIV i-Base

Numerous studies at this workshop explored the potential for indiviudalised dosing with atazanavir, relating to individual patient absorption, the use of ritonavir boosting ands interations with HIV and TB medications.

Atazanavir is widely used because it is generally well tolerated, has a low pill count and only requires once-daily dosing. Ritonavir boosting is routinely recommended to maximise drug exposure, and to reduce the risk of low trough levels and interpatient variability. However, higher atazanavir exposure is related to risk of hyperbilirubinaemia and the ritonavir boosting negatively impacts on lipid profiles.

As with efavirenz, the study from Columbo and collegues that identified genetic polymorphisms associated with absorption showed a higher rate of discontinuation of atazanavir due to side effects in patients with compared to those without these markers (52% vs. 20%, p=0.008). [1]

Taburet and colleagues reported results from a substudy (n=15) of the INDUMA trial where treatment naive patients were prescribed atazanavir/ritonavir (300mg/100mg QD) plus 2 nukes (not including tenofovir) and then randomised to continue on the same regimen or switch to unboosted atazanavir (400mg), maintaining the nukes. [2]

Atazanavir levels (adjusted geometric mean ratios) for Cmin and AUC dropped by 10% (5.8-19%) and 34% (26-46%) from the switch (week 0) and after 4 weeks on the reduced regimen. As expected, all PK parameters reduced without boosting and interpatient variability increased (see Table 1).

Table 1. Atazanavir levels: geometric mean (CV%) with and without ritonavir boosting

	week 0 ATZ/r 300/100	week 4 ATZ 400
Cmax (ng/mL)	3317 (39%)	1895 (69%)
Ctrough (ng/mL)	543 (92%)	64 (125%)
AUC 0-24 (ng*h/mL)	35617 (52%)	12197 (81%)

However, despite the reduced atazanavir levels, 14/15 patients maintained viral suppression <50 copies/mL at 48 weeks, with only one patient experiencing a blip (to 113 copies/mL).

Regazzi and colleagues presented results from using therapeutic drug monitoring in treatment-experienced patients using atazanavir, with and without ritonavir. [3]

The target range for atazanavir is 150-850 ng/mL.

The group analysed samples from 170 patients (with and without HCV coinfection) using various dosing regimens including ATZ/r 300/100 QD (n=79), ATZ 400 QD (n=57), ATZ 300 QD (n=11), ATZ/r 400/100 (n=5), ATZ 400 BID (n=8) and ATZ/r 200/100 QD (n=10). The main comparison between ATZ/r 300/100 QD and ATZ 400 QD showed lower atazanavir exposure and wider interpatient variability (CV%) without ritonavir (see Table 2).

Although both regimens showed similar levels of viral suppression (~84%), significant differences were seen between patients with or without HCV coinfection.

With the 400mg QD regimen, monoinfected patients experienced significantly lower trough levels (240 [100-400] vs. 600 [400-950] ng/mL, p<0.001). Conversely, coinfected patients using 400mg QD achieved similar trough levels to both mono- and coinfected patients using the 300/100mg dosing.

The authors do not comment on why this may be the case and it is unclear whether this was a real effect directly relating to coinfection or possible confounding with drug use or adherence (if IDUs were less adherent, they would tend to have lower trough levels).

Guillemi and colleagues from British Columbia looked at using TDM to indentify patients with high atazanavir trough levels (>900 ng/mL using ritonavir boosting) and then to confirm unboosted levels were >150 ng/mL prior using 400mg unboosted as a maintenance dose. [4]

They identified 20 patients (14 using tenofovir/FTC and 6 using abacavir/3TC) with baseline median [IQR] trough level of 1369 [1090-1620] ng/mL. Median trough level after 7-10 days on 400mg ATZ (unboosted) was 173 [96-301] ng/mL. CD4 was unchanged and no patient experienced viral rebound, although total bilirubin levels significantly declined (from 52 [28-64] to 18 [12-24] umol/L, p<0.001).

Table 2. Atazanavir exposure with and without ritonavir

	ATZ/r 300/100mg QD	ATZ 400mg QD
Ctrough ng/mL, mean [IQR] (CV%)	720 [430-1200] (79%)	340 [130-600] (147%)
% <150	3.8%	30%
% 150-850	57%	54%
% >850	39.2%	15.8%
% viral load <50 copies/mL	84.8 %	84.2%

The 9/20 patients with Ctrough <150 ng/mL (4 on abacavir, 5 on tenofovir) were switched back to the 300/100 boosting regimen while 11/20 continued on 400mg QD unboosted atazanavir.

A second study from the same group looking at the relationship between tenofovir use and unboosted atazanavir levels and showed that some patients maintained undetectable viral load despite trough level <150 ng/mL. [5]

The mdian atazanavir trough level in 43 patients was 242 (range 106-1100) ng/mL. Four patients with low trough levels (107-131 ng/mL) increased their dose to 600mg QD, resulting in trough increases to 222-294 ng/mL).

Of 31 patients with undetectable viral load at baseline, 30/31 remained <50 copies/mL.

Atazanavir and raltegravir

Two studies looking at the interaction between raltegravir and atazanavir suggest that individual monitoring is likely to be important when considering using these drugs in the same combination.

Molto and colleagues presented results from a study in 15 HIV-positive patients (4 women) who added raltegravir 800mg once-daily for 10 days, to the regimens of patients already using 400mg atazanavir once-daily for at least the previous two weeks. Use of tenofovir or proton pump inhibitors was not permitted. Both drugs were given with a light meal.

Previous studies have shown that atazanavir inhibits raltegravir metabolism by UGT1A1, boosting raltegravir exposure.

The geometric mean ration (95%CI) for Cmax and AUC 0-24 were compared with historical data on 20 HIV-negative individuals receiving raltegravir with a high fat meal.

Mean (IQR) raltegravir values for Cmax, Tmax, AUC0-24h and Ctrough were 5.36 (3.22-8.91 uM/mL, 2.95 (2.09-4.18) hours, 29.04 (20.46-41.22) uM*h/mL and 69.53 (39.58-122.16) nM/mL respectively. Raltegravir Ctough was <33nM in four patients.

Compared to historical controls using a single 400mg dose of raltegravir GMR (95%CI) for Cmax, AUC 0-24h and Ctrough were 2.81 (1.43-5.50) p=0.004; 1.18 (0.74-1.88) p=0.465 NS and 0.15 (0.07-0.32) p<0.001 respectively. The comparisons were not normalised for comparing the 400mg and 800mg dose, so the practical use of information about the almost 3-fold higher Cmax and 85% reduction in Ctrough are unclear. [6]

Ripamonti and colleagues presented what was perhaps a more pharmacologically useful study. This group switched 21 HIV-positive patients to twice-daily atazanavir (200mg without ritonavir-boosted) plus raltegravir (400mg twice-daily), due to either drug resistance or tolerability on their current regimen. [7]

PK results after at least 2 weeks on the new combinatin showed wide interpatient variability for parameters of both durgs. The geometric mean (95%CI) for atazanavir AUC0-12h, Cmax and Cmin were 6257 (4334-8172) ng*h/ML, 1062 ng/mL (676-1448) ng/mL and 227 (122-332) ng/mL respectively. The geometric mean (95%CI) for raltegravir AUC0-12h, Cmax and Cmin were 9085 (6317-11,854) ng*h/ML, 2402 ng/mL (1496-3308) ng/mL and 132 (1-263) ng/mL respectively. Five patients had atazanaivr levels below the minimum target of 150 ng/mL. About 60% of patients entered the study with undetectable viral load, which was achieved by all patients two weeks after the switch, though these results need to show durability before and comment can be made about efficacy of the combination.

Of concern, the investigators concluded that this combination 'may' provide adequate plasma concentrations for 'some' patients. Clearly the only reliable way to identify thos patinets is through using TDM on an individual basis.

Drug interaction studies with atazanavir and non-HV drugs included an antimalarial study (see article above). [8]

C O M M E N T

While ritonavir boosting clearly improves atazanavir levels, the results from these studies indicate that for some patients, when supported by TDM, there may be an option to maintain viral suppression on an unboosted regimen.

The wide interpatient variability appears to protect some patients even when druginteractions are known to reduce theraputic levels.

For other combinations, notably with raltegravir, and especially when using novel dosing, TDM seems essential.

References

Unless otherwise stated all references are to the Programme and Abstracts of the 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam.

1. Colombo S et al. Association of pharmacogenetic markers with premature discontinuation of first-line ART. Oral poster O-03.
2. Taburet A et al. Pharmacokinetics of atazanavir administered once daily with or without ritonavir in HIV infected patients: INDUMA Study. Poster abstract P-32.
3. Regazzi M et al. Therapeutic monitoring and variability of atazanavir in experienced HIV-infected patients receiving boosted or unboosted regimens. Poster abstract P-35.
4. Guillemi S et al. A short trial of unboosted atazanivir in patients receiving atazanavir/ritonavir with high trough levels to select candidates for unboosted atazanavir maintenance therapy. Poster abstract P-46.
5. Harris M et al. Atazanavir trough levels in patients receiving unboosted atazanavir and tenofovir. Poster abstract P-21.
6. Molto J et al, Pharmacokinetics and safety of once-daily raltegravir (800mg) plus atazanavir (400mg) in HIV-infected patients. Oral abstract O-13.
7. Ripamonti D et al. Steady-state pharmacokinetics of atazanavir (200mg BID) when combinaed with raltegravir (400mg BID) in HIV-infected adults. Oral abstract O-14.
8. Ref: Van Luin M et al. Drug interactions between atovaquone/proguanil and antiretroviral agents. Oral poster O-19.

Raltegravir PK in blood plasma and the genital tract

Simon Collins, HIV i-Base

Jones and colleagues from University of North Carolina presented results of an open label single-arm pharmacokinetic study in seven HIV-negative women, comparing drug levels in blood plasma (BP) and cervical vaginal fluid (CVF) following standard dose raltegravir (400mg BID). [1]

Raltegravir was taken with a 545 kcal meal (18% fat, 70% carbs, 12% protein) and nine paired samples were taken on day one and day seven.

Although median levels achieved in CVF were 63% and ~100% of those in BP at day 1 and seven respectively (see Table 1), the IQR for the CVF:BP ratios showed such a wide interpatient variability crossing 1.0 that this couldn't be relied on for individual patient results [0.26-1.91 and 0.41-1.69 respectively].

Notably, elimination was slowed in CVF with a two-fold increase in half life (7 [5-12] vs. 17 [14-23] hours) compared to BP. Steady-state was reached after 2 days in BP and 4 days in CVF.

Table 1: Median {IQR] raltegravir levels in BP and CVF

	BP	CVF
Day 1		
Cmax (ng/mL)	790 [249-2585]	631 [327-1658]
C12h (ng/mL)	55 [10-255]	607 [321-1283]
AUC 0-12h (ng*hr/mL)	3393 [717-7322]	1677 [910-66,716]
Tmax (hr)	6 [3-6]	12 [8-12]
Day 7		
Cmax (ng/mL)	1874 [403-2200]	1272 [879-2388]
C12h (ng/mL)	19 [10-31]	282 [142-523]
AUC 0-12h (ng*hr/mL)	11,911 [6979-15,998]	9769 [2238-19649]
Tmax (hr)	8 [6-12]	3 [0.5-3.0]

C O M M E N T

Bearing in mind these data are only showing IQR in a very small sample of women, the pharmacokinetics of raltegravir at steady state, show at least a 10-fold interpatient range in most parameters, in both BP and CVF.

Ref: Jones A et al. First-dose and steady-state pharmacokinetics (PK) of raltegravir in the genital tract of HIV uninfected women. 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam. Oral abstract O-06.

A CYP2B6 haplotype influences nevirapine plasma concentrations following a single dose to reduce mother to child transmission

Polly Clayden, HIV i-Base

Tim Cressey from the Program for HIV Prevention and Treatment (PHPT), Chaing Mai, Thailand and Harvard School of Public Health, Boston, USA presented data from an evaluation of the association between single nucleotide polymorphisms (SNP) and haplotypes within CYP2B6, CYP3A4 and ABCB1, and nevirapine (NVP) plasma concentrations in Thai women following single dose NVP as part of HIV mother to child transmission prophylaxis. [1]

Currently, pregnant HIV-positive women that do not reach eligibility criteria for antiretroviral treatment in Thailand receive AZT from 28 weeks gestation and intrapartum single dose NVP to reduce mother to child transmission. Persistence of NVP in plasma following a single dose has been demonstrated to select for NNRTI mutations, which, in turn, can compromise subsequent NNRTI containing HAART.

In this study, investigators from Thailand and the USA, used plasma and DNA samples from 330 women who had received single dose NVP in the PHPT-2 trial. [2] Nine SNPs within CYP2B6, CYP3A4 and ABCB1 were genotyped using real time PCR. Data from 640 plasma samples taken between delivery and 21 days post partum were available.

Nevirapine plasma concentrations were determined by high-performance liquid chromatography and used in a population pharmacokinetic analysis.

For the CYP2B6 516G>T polymorphism, the investigators found, 43.0% (n=142), 46.7% (n=154) and 10.3% (n=34) of women had

G/G, G/T and T/T genotypes, respectively. Nevirapine exposure was higher in women carrying the CYP2B6 516G>T polymorphism but this was not statistically significant, p=0.054.

Two tag-SNPs in CYP2B6: g.18492T>C and g.21563C>T, were significantly associated with NVP AUC, p=0.041 p=0.019 respectively.

The mean (SD) NVP AUC was 154.7 (33.7), 160.9 (33.3) and 17.7 (34.4) mcg.hr/mL in women with g.21563C/C C/T and T/T genotypes, respectively, p=0.27.

When they performed a haplotype analysis of CYP2B6 at 5 loci they found that the TGATC haplotype (g.3003T>C, 516G>T, 785A>G, g.18492T.C and g.21563C>T) was significantly associated with NVP AUC, p=0.00061.

The mean (SD) NVP AUC was 164.5 (33.8, n=197), 152.7 (33.9, n=114) and 146.1 (23.9, n=19) mcg.hr/mL for women with non-TGATC, TGATC-heterozygous and TGATC-homozygous genotypes respectively, p=0.0029.

The median time for NVP concentrations to reach 10 ng/mL postpartum was 18 (IQR 14-21) days, 16 (IQR 13-20) days and 14 (IQR 14-19) days for women with non-TGATC, TGATC-heterozygous and TGATC-homozygous genotypes respectively, p=0.02.

No other genetic polymorphisms evaluated in this analysis were significantly associated with NVP AUC.

CYP2B6 516G>T has previously been shown to affect NVP oral clearance during chronic treatment. The investigators observed that CYP2B6 516G>T seems to have a more modest impact on single dose NVP than on NVP used in chronic treatment. They suggest that the physiological changes experienced during pregnancy and/or the minimal autoinduction of CYP3A4 and 2B6 enzymes following a single dose compared to steady state (1.5 to 2-fold increase in NVP CL/F during first two weeks of treatment) may explain this observation.

They concluded that CYP2B6 polymorphisms following single dose NVP may account for some of the interpatient variability observed in post partum NVP concentrations but that the clinical significance of this finding may be relatively small.

Ref: Chantarangsu S et al. A CYP2B6 haplotype influences nevirapine plasma concentrations postpartum following a single intrapartum dose for the prevention of mother to child transmission of HIV in Thai women. 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam. Abstract O_02.

Population pharmacokinetic model of nevirapine maternal to infant transfer through breastfeeding

Polly Clayden, HIV i-Base

Edmund Capparelli from the University of California, San Diego, USA, presented a population pharamcokinetic (PK) model of nevirapine (NVP) concentrations in maternal plasma, breast milk and infant dried blood spots (DBS) to better characterise infant NVP exposure via breast milk.

This analysis used data collected in a previously published substudy of the Kisumu breastfeeding study in Kenya (in which pregnant women received NVP-containing HAART to prevent mother to child transmission via breastmilk), the substudy measured antiretroviral concentrations in maternal plasma, breastmilk and infant DBS in 67 mother and infant pairs. There were 153 paired plasma and breast milk samples and 191 DBS samples.

The investigators performed PK modelling using the NONMEM programme. They developed a semi-physiologic population model to describe maternal plasma and breast milk concentrations simultaneously. These were linked with infant feeding times in order to estimate breast milk NVP concentrations at the time of feeding. In turn these breast milk concentrations were used to estimate NVP doses for the infant PK model of DBS concentrations.

Liquid chromatography mass spectrometry was used to measure NVP concentrations in the samples. The limits of quantification of the assay were 17ng/mL for plasma and breast milk, 40ng/mL for DBS and 43ng/mL for NVP.

The analysis found maternal plasma NVP PK parameters were stable during the study period. Breast milk and plasma NVP concentrations reached equilibrium rapidly, relative to elimination, providing relatively stable breast milk: plasma ratio with breast milk concentrations above the IC50 throughout the dosing interval.

The investigators reported an overall population NVP breast milk: plasma of 0.74. The typical estimated PK parameters for infants were: CL/F 0.0265 (+/-0.003)L/h/kg and V/F 0.97 (+/-0.125) L/h/kg. CL/F among infants increased with age giving lower median DBS concentrations at 14 weeks (717ng/mL) compared to 2-6 weeks of age (1005ng/mL).

They concluded that infant NVP exposure via breastfeeding achieves prophylactic concentrations as seen in the first weeks of age with PMTCT dose (2mg/kg). They noted that, “NVP breast milk concentrations rapidly equilibrate with maternal system concentrations and while slightly lower than plasma were well in excess of therapeutic NVP concentrations”. Also that the variability in both maternal and infant NVP elimination contributes more to infant exposure than NVP the breast milk:plasma ratio variability.

Ref: Capparelli et al. Population pharmacokinetic model of nevirapine (NVP) maternal to infant transfer through breastfeeding. 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam. Abstract 0_18.

Phenotypic and genotypic inhibitory quotients and virologic response in treatment experienced children

Polly Clayden, HIV i-Base

Natella Rakhmanina from the children's National Medical Center, Infectious Diseases, Special Immunology and Pharmacology, Washington, showed findings from a study to investigate whether the lopinavir (LPV) phenotypic inhibitory quotient (PIQ) and genotypic inhibitory quotient (GIQ) in treatment experienced children correlate with treatment response, when receiving LPV containing HAART, as observed in treatment experienced adults.

In this study the investigators collected 52 weeks prospective data from children and adolescents aged 4-15 years receiving LPV/r as single PI within antiretroviral regimens. 12-hour pharmacokinetic (PK) samples were collected and LPV susceptibility measured within 3 months of enrollment. Treatment histories, including resistance information, were obtained from medical records. Viral load and self reported adherence were measured 3 monthly.

IQ was calculated as the rate of plasma 12-hour trough concentration (Cmin) after observed dose divided by the protein-adjusted IC50 for PIQ and the number of LPV-associated mutations for GIQ.

In this analysis, 45 PI experienced children and adolescents were followed for 52 weeks. Their median age was 11 (5.3-17.8) years; 24 were girls and the majority (n=41) were African American. Of the group 40 (89%) received background regimens of 2 NRTIs, 2 received 3 NRTIs and 3 received NRTI plus NNRTI.

The median length of PI experience was 5.2 (0.7-9.2) years and of previous LPV exposure was 2.2 (0.5-5.0) years. Self reported adherence was a mean of 88% (41-100%). About half, 24/45(53%), of the patients achieved viral load, 400 copies/mL, at least once during the study. The median LPV Cmin was 6.2 (0.1- 16.7) mg/L.

Median PIQ (n=36) was 12.6 (0.03-231.1). The investigators noted that a baseline PIQ cutoff of 15 (as in adults) did not distinguish those achieving a viral load of <400 copies/mL from those that did not, p=0.09.

In multivariate analysis, only baseline PIQ >25 was significantly associated with viral load <400 copies/mL: 11/16 (69%) patients with PIQ >25 achieved viral load <400 copies/mL vs. 5/20 (20%) with PIQ <25, p=0.01.

The geometric mean PIQ in those patients achieving viral load <400 copies/mL was 16.7 vs 2.4 in those who did not, p=0.09.

The investigators found for every increase in baseline PIQ of 10, the probability of achieving viral load <400 copies/ml, when adjusted for prior duration of LPV treatment, increased 9.6-fold (95% CI 9.2-9.9), p=0.02.

They reported a median GIQ (n=22) of 1.0 (0.03-6.5) and a median of 6 (1-13) LPV mutations per patient. The geometric mean GIQ in those achieving viral load <400 copies/mL was 1.0 vs. 0.7 in those who did not, p=0.56.

The investigators concluded that LPV PIQ was associated with viral load <400 copies in PI experienced HIV-positive children and adolescents but GIQ was not. They suggest that a cutoff of LPV PIQ >25 may be a target for maximising efficacy.

Ref: Rakhmanina N et al. The phenotypic and genotypic susceptibility lopinavir scores and virologic response in treatment experienced children with HIV. 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam. Abstract 0_17.

Tenofovir pharmacokinetics in three tenofovir-containing regimens in children and adolescents

Polly Clayden, HIV i-Base

J King and coworkers reported pharmacokinetc (PK) parameters of tenofovir (TDF) tablets received in combination with efavirenz (EFV) or duranavir/ritonavir (DRV/r) or atazanavir/ritonavir (ATV/r) in a group of children and adolescents age 8-18 years.

This study enrolled patients receiving >=2 weeks TDF 300mg in combination with:

Arm 1: EFV 300mg or 600mg once-daily

Arm 2: DRV/ritonavir dosed at 300/100 or 600/100 twice-daily

Arm 3: ATV/ritonavir dosed at 200-400mg/100mg twice-daily

Plasma samples were taken at 0, 1, 2, 4, 6, 8, 12 and 24 hours post dose and plasma concentrations of TDF were measured.

The investigators performed statistical tests to evaluate whether the 90% confidence intervals of the geometric mean (GM) for the PK parameters of TDF were within the target range ie 0.5-2.0 fold of adult values: 2.8 (2.3-3.6) mgxh/L and 0.06 (0.05-0.08) mg/L AUC and Cmin respectively.

They found that among patients receiving EFV (n=15) the TDF GM (90% CI) AUC and Cmin were 2.9 (2.4-3.4) mg.h/L and 0.07 (0.05-0.09) mg/L respectively. AUC and Cmin were 3.1(2.4-4.0) mg.h/L and 0.07 (0.05-0.09) mg/L in patients receiving DRV/r (n=10) and 3.6 (3.0-4.5) mg.h/L and 0.07 (0.06-0.10) mg/L respectively in patients receiving ATZ/r (n=17).

They noted that the TDF Cmin 90% CI included values above the target upper limit of 0.08 mg/L in all three arms and the AUC 90% CI included values above the upper target limit of 3.6 mg.h/L in patients receiving DRV/r or ATV/r.

The investigators concluded: "These data suggest that DRV/r and ATV/r may increase TDF exposure in HIV-infected children and adolescents."

Ref: King J et al. A comparison of tenofovir pharmacokinetics across three tenofovir-based antiretroviral regimens in HIV-infected children and adolescents. 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam. Abstract P_53

Bioavailability of Thai generic lopinavir/ritonavir

Polly Clayden, HIV i-Base

A poster authored by J van der Lugt and coworkers from Thailand and the Netherlands described pharmacokinetic (PK) data and short-term safety of a generic lopinavir/ritonavir (LPV/r) 200/50mg formulation tablet. [1]

In this study, patients receiving PI based therapy with viral load <50 copies/mL were switched to generic LPV/r 400/100mg twice daily. Trough concentrations (Cmin) were measured prior to the switch in 16 patients receiving Kaletra and 4 weeks after the switch in all patients.

Plasma levels of LPV and RTV were measured using high performance liquid chromatography with a lower limit of quantification of 0.1mg/L for LPV and 0.045mg/L for RTV.

A group of 37 patients were evaluated in this study; their mean (SD) weight was 60.3 (11.8) kg and18 were women. Two patients discontinued the study medications due to intolerance.

The investigators reported the mean (SD) Cmin of LPV was 7.3 (1.8) mg/mL. None of the patients evaluated had subtherapeutic levels. They found no difference in LPV Cmin in patients receiving Kaletra before switching to the generic formulation of LPV/r, p=0.21. However, the Cmin of the generic RTV was higher than that reported for Kaletra, p=0.019. They found the coefficient of variation was 25% for the tablet formulation and 54% for the Kaletra. They noted that these values did not appear to be affected by food intake.

They concluded: "These data support the efforts in scaling up access to generic second line treatment in middle and low income countries."

C O M M E N T

There are currently limited protease inhibitors available for second line treatment in low and middle-income countries. Although originator LPV/r (Kaletra/Aluvia) is the most common protease inhibitor in industrialised countries, generic LPV/r is not widely used in resource limited settings as there have been concerns about the quality (including studies by the originator company) and limited data. [2]

These data are reassuring, as is the FDA tentative approval in March this year of Indian generic versions of LPV/r manufactured by Aurobindo and Matrix Laboratories. [3]

Studies of a paediatric "sprinkle" formulation from Cipla are underway.

References

1. van der Lugt J et al. Bioavailability of generic lopinavir/ritonavir in HIV-1 infected individuals. 10th International Workshop on Clinical Pharmacology of HIV Therapy, 15-17 April 2009, Amsterdam. Abstract P_41.
2. Garren KW et al. Bioavailability of Generic Ritonavir and Lopinavir/ritonavir Tablet Products in a Dog Model Abbott Laboratories, Abbott Park, IL. 2nd International Workshop on HIV Treatment, Pathogenesis and Prevention Research in Resource-Poor Settings, 20-23 May 2008, Dakar, Senegal.
3. http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm

CONFERENCE REPORTS

XVIII International Drug Resistance Workshop

9-13 June 2009, Florida

Introduction

The following reports from the 2009 International Drug Resistance Workshop are included from NATAP.org.

- Transmitted multidrug-resistant HIV persists in PBMC DNA for years
- Low-level Q148R in people without integrase inhibitor experience
- Cut-offs suggested for predicting efavirenz failure with low-level K103N
- Lower M184V rates with FTC/TDF than with 3TC/TDF
- HBV resistance to lamivudine at undetectable and low levels of viremia

Transmitted multidrug-resistant HIV persists in PBMC DNA for years

Mark Mascolini for natap.org

When acquired during primary infection, HIV resistant to the first 3 antiretroviral classes may persist for years in peripheral blood mononuclear cell (PBMC) DNA, according to results of a 5-person substudy [1] in the French PRIMO cohort [2].

Viral coreceptor use also remained unchanged after primary infection in these people.

Jade Ghosn (Universite Paris Descartes) and colleagues genotyped HIV and determined coreceptor use in plasma HIV RNA and in HIV DNA extracted from PBMCs of 5 people infected with triple-class-resistant virus and monitored for at least 18 months. After testing primary infection samples, the investigators repeated the analyses at 6 or 12 months, then every 12 months. They defined triple-class resistance as mutations conferring resistance to at least one drug in the first three antiretroviral classes. Ghosn and colleagues determined viral coreceptor use in cellular DNA by a combination of five genotype-based algorithms.

Five people infected between 1996 and 2006 had virus with the coreceptor preferences and primary resistance mutations in reverse transcriptase (RT) and protease (PRO) detailed in Table 1.

Patient A began successful therapy 30 months after infection, yet all resistance mutations persisted in PBMC DNA for 78 months (6.5 years), except for K103N, which reverted to wild-type at month 60. Use of the CXCR4 coreceptor remained unchanged in viral DNA to month 78.

Table 1: Coreceptor use and resistance mutations in 5 patients

Patient No.	Coreceptor	RT mutations	Protease mutations
Pt A	CXCR4	41L, 103N, 118I, 210W, 215Y	63P, 90M
Pt B	CCR5	67N, 69N, 70R, 103N, 108I, 116Y, 151M, 184V, 215V, 219Q	10F, 36I, 46I, 82A
Pt C	CXCR4	41L, 67N, 69D, 74V, 115F, 118I, 179V, 184V, I88L, 210W, 215F	10V, 20R, 32I, 33F, 36L, 46I, 47A, 62I, 63P, 71V, 82A, 90M
Pt D	CXCR4	67N, 69N, 70R, 118I, 181C, 215F, 219Q	10I, 20R, 36I, 54V, 82A, 90M
Pt E	CCR5	67N, 69D, 70R, 103N, 184V, 219Q, 225H	10I, 36I, 46L, 53L, 54V, 63P, 71V, 82A

Patient B began successful therapy and at month 6 genotyping could not be performed in plasma. This patient's mutation pattern remained unchanged in PBMC DNA through 2 years of follow-up, and the virus continued using CCR5.

Patient C began successful therapy but had an essentially unchanged mutation pattern in PBMC DNA for 12 months.

Patient D began treatment soon after diagnosis, and HIV RNA fell to undetectable levels within 6 months. Resistance mutations persisted in HIV DNA and virus remained X4 through 84 months of follow-up.

Patient E kept the same mutation pattern in HIV RNA and DNA for 36 months after infection, except for the M184V mutation, which reverted to wild-type in HIV RNA at month 12. But M184V persisted in HIV DNA throughout 36 months of follow-up. Coreceptor use did not change from CCR5 in HIV RNA or DNA through month 36.

Overall, multidrug-resistant virus persisted in these 5 people for a median of 78 months. Ghosn and colleagues proposed that persistence of coreceptor preference in RNA and DNA indicate early expansion of a monoclonal viral population.

References
1. Ghosn J, Galimand J, Meyer L, et al. Long-term persistence of resistance mutational pattern and evolution of HIV-tropism in blood plasma and in infected cells of patients who acquired a multidrug-resistant HIV-1 strain at the time of primary infection. XVIII International Drug Resistance Workshop. 9-13 June 2009, Fort Myers, Florida. Abstract 86.
2. Chaix ML, Descamps D, Wirden M, et al. Stable frequency of HIV-1 transmitted drug resistance in patients at the time of primary infection over 1996-2006 in France. AIDS. 2009;23:717-724.

Low-level Q148R in people without integrase inhibitor experience

Mark Mascolini for natap.org

Minority populations of the Q148R integrase mutation could be found in most integrase-inhibitor-naive people studied by Charlotte Charpentier and colleagues in Paris. [1]

The study yielded two other interesting findings:

- Low-level Q148R did not affect response to raltegravir in a large majority of people who started that integrase inhibitor.
- Experience with other antiretrovirals had no apparent impact on prevalence of low-frequency Q148R.

Charpentier and coworkers used allele-specific PCR that can detect Q148R representing only 0.10% of a person's viral population. Q148R may make HIV resistant to raltegravir or elvitegravir. [2, 3]

The investigators probed viral samples from two groups--40 people with heavy antiretroviral experience but without integrase inhibitor experience, and 51 people who never took any antiretrovirals. The supersensitive PCR assay proved successful in 74 of the 91 viral samples (82%). Most of the samples that could not be amplified were HIV-1 subtypes other than B. Charpentier also used a highly sensitive K103N assay to probe for minority populations of this nonnucleoside mutation in 47 of the antiretroviral-naive people.

Among 32 antiretroviral-experienced people whose viral sequences could be amplified, 26 (81%) had detectable Q148R at a median frequency of 0.40% (range 0.15% to 0.92%). Among 42 antiretroviral-naive people, allele-specific PCR spotted minority clusters of Q148R in 36 (86%), a proportion close to that in the antiretroviral-experienced group. Q148R turned up at a median frequency of 0.46% (range 0.13% to 1.98%) in the untreated people.

Allele-specific PCR uncovered low-frequency K103N in 12 of 47 antiretroviral-naive people (26%). Thus minority Q148R variants were significantly more common in both groups of integrase inhibitor-naive people than minority K103N variants were in naive people ($P < 0.0001$).

Of 26 people with detectable but low-frequency Q148R who started a raltegravir salvage regimen, 24 (92%) responded with a viral load below 40 copies. Twenty of these 24 responders reached an undetectable load within 12 weeks of starting raltegravir, while the other 4 attained undetectable viremia between week 18 and week 36.

In the 2 people whose raltegravir regimen failed, the resistance pathway began with Q148R, which emerged as a majority population within 3 months of starting the integrase inhibitor. Everyone without low-frequency Q148R before raltegravir-based salvage responded to their regimen.

Charpentier and colleagues suggested that "the high prevalence of minority Q148R variants found in antiretroviral-experienced patients is not the consequence of a history of long-term reverse transcriptase inhibitor-containing therapies, since similar data are found in antiretroviral-naive patients."

References
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2. Waters J, Margot N, Hluhanich R, et al. Evolution of resistance to the HIV integrase inhibitor (INI) elvitegravir can involve genotypic switching among primary INI resistance patterns. XVIII International Drug Resistance Workshop.9-13 June 2009, Fort Myers, Florida. Abstract 116.
3. Johnson VA, Brun-Vezinet F, Clote B et al. Update of the drug resistance mutations in HIV-1: spring 2008. Top HIV Med. 2008;16:62-68.

Cut-offs suggested for predicting efavirenz failure with low-level K103N

Mark Mascolini for natap.org

Studies of virologic outcome in people who begin a nonnucleoside with low-frequency K103N mutations yielded conflicting results. [1-3]

A new analysis of low-level K103N in people starting efavirenz in a trial comparing tenofovir/emtricitabine (TDF/FTC) with zidovudine/lamivudine (AZT/3TC) suggested that more than 2000 copies/mL of K103N before efavirenz – or K103N making up more than 2% of the viral population – independently boosts the odds of virologic failure. [4]

Evguenia Svarovskaia and Gilead Sciences colleagues analyzed the impact of K103N on virologic response in 509 people enrolled in GS-01-934. The original primary efficacy analysis excluded 22 people (4%) in whom standard genotyping detected a nonnucleoside mutation before treatment began. Of the remaining 487 study participants, 48 (10%) with resistance data available endured virologic failure through week 144, including 19 taking TDF/FTC and 29 taking AZT/3TC.

The Gilead team reanalysed these 487 pretreatment viral samples with an allele-specific PCR assay that detects K103N representing as little as 0.5% of a person's viral population. Almost all of those samples – 476 of 485 (98%) – yielded allele-specific PCR results. Sixteen of those 476 (3%) had detectable K103N missed by standard sequencing. Thus, the percentage of all study participants with a NNRTI mutation before treatment rose to 7.5% (38 of 509 samples).

Among the 16 people with low-level K103N, efavirenz failed in 6 (37.5%), including 5 taking AZT/3TC and 1 taking TDF/FTC. Pretreatment K103N correlated strongly with virologic failure in the 5 people taking AZT/3TC with efavirenz (p=0.005).

In these 16 people with low-frequency K103N, the percentage of K103N detected by the ultrasensitive assay and K103N copy count were higher in the 6 with virologic failure (0.8% to 15%, 1254 to 16,071 copies/mL) than in the 10 virologic successes (0.6% to 3.2%, 51 to 5535 copies/mL). Five of 6 people with more than 2000 copies/mL of K103N had a virologic failure, compared with 1 of 10 people without virologic failure, a significant difference (p=0.008). Efavirenz plus TDF/FTC failed in 1 person with a K103N load under the 2000 mark (1254 copies/mL), but this person began treatment with a CD4 count of only 20.

Multivariate statistical analysis that considered predictors as categorical variables determined that a K103N copy number at or above 2000 copies/mL hoisted the risk of virologic failure nearly 50 times (odds ratio [OR] 47.4, 95% confidence interval [CI] 5.2 to 429.2, p=0.0006). In the same analysis, randomization to TDF/FTV versus AZT/3TC, pretreatment viral load above 100,000 copies, and pretreatment CD4 count above 199 did not independently predict failure. In a similar analysis, K103N making up more than 2% of a person's viral population upped the failure risk 25 times (OR 25.5, 95% CI 4.6 to 142.1, p=0.0002).

Svarovskaia and coworkers suggested their findings point to a pretreatment K103N threshold that predicts virologic failure with efavirenz. However, that conclusion rests on a sample of only 16 people. The investigators point out that only 6 of 476 study participants with allele-specific PCR results (1.3%) had a pretreatment K103N population above 2000 copies/mL.

References

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Lower M184V rates with FTC/TDF than with 3TC/TDF

Mark Mascolini for natap.org

Using tenofovir (TDF) or a ritonavir-boosted protease inhibitor (PI) with emtricitabine (FTC) may slow emergence of the M184V mutation with emtricitabine (FTC), according to results of cell-study and cohort analyses by Valentina Svicher and colleagues at the University of Rome Tor Vergata and Catholic University in Leuven, Belgium [1]. The investigators also confirmed their clinical observation of less frequent M184V emergence with FTC/TDF than with lamivudine (3TC)/TDF or 3TC without TDF.

Svicher and coworkers analysed 1337 HIV-1 subtype B *pol* gene sequences from three groups, each of which included people taking their first regimen and people taking a later regimen:

- 168 people treated with FTC/TDF (35 first-line, 133 later)
- 249 people treated with 3TC/TDF (27 first-line, 222 later)
- 920 people treated with 3TC but naive to TDF (165 first-line, 755 later)

The three patient groups were similar in clinical and virologic characteristics, except for two: A significantly lower proportion of FTC/TDF patients took a nonnucleoside with their regimen (27.4%) when compared with the 3TC/TDF group (37.7%) or the 3TC-only group (39.0%) (p=0.02), and a significantly higher proportion in the FTC/TDF group took a PI (70.2%) than did people in the 3TC/TDF group (47.8%) or the 3TC-only group (48.5%) (p<0.001).

When these regimens failed as first-line therapy, no nucleoside-related mutations emerged in 82.9% of those taking FTC/TDF, in 51.8% of those taking 3TC/TDF, and in 47.9% of those taking 3TC but not TDF (p=0.02).

M184V emergence proved less frequent in people treated with FTC/TDF than in those treated with 3TC/TDF or those treated with 3TC without TDF. This lower rate held true in people with multidrug experience (45.9%, 61 of 133, with FTC/TDF; 59.4%, 132 of

222 with 3TC/TDF; 71.9%%, 543 of 755 with 3TC alone, p<0.01) and in people whose first regimen failed (11.4%, 4 of 35 with FTC/TDF; 25.9%, 7 of 27 with 3TC/TDF; 51.0%, 84 of 165 with 3TC alone, p<0.001).

Overall prevalence of M184V was 38.7% with FTC/TDF, 55.8% with 3TC/TDF, and 68.0% with 3TC without TDF.

Statistical analysis considering numerous factors that may affect emergence of M184V found that two variables independently raised the risk of that mutation:

- Prior 3TC use more than doubled the risk: odds ratio (OR) 2.28, 95% confidence interval [CI 1.74– to 2.98, p<0.001)
- Use of zidovudine or stavudine raised the risk 66%: OR 1.66, 95% CI 1.16 to 2.38, p=0.004)

Two factors independently made emergence of M184V less likely:

- TDF use: OR 0.60, 95% CI 0.42 to 0.88, p=0.008
- Boosted-PI use: OR 0.50, 95% CI 0.33 to 0.75, p=0.0009

To elicit resistance mutations, the investigators exposed HIV in CEM cells to increasing doses of 3TC (0.025 to 0.25 microM) and FTC (0.025 to 0.25 microM) with or without TDF (1.25 to 10 microM). In these selection experiments, M184V did not emerge in up to 10 passages over 2 months with 3TC/TDF or FTC/TDF, a finding confirming the protective role of TDF.

The T69I mutation evolved in selection experiments with 3TC/TDF but not with FTC/TDF. When T69I arose without M184V in treatment-experienced patients in the Stanford database, it conferred 74.5-fold resistance to 3TC (p=0.03). But T69I was rare in these patients, arising in only 4 of 432 (0.4%) of those in whom 3TC/TDF failed.

Svicher and coworkers suggested three explanations for less frequent M184V emergence with FTC/TDF than the other two regimens: greater potency of FTC than 3TC, different intracellular pharmacokinetics of FTC triphosphate than of 3TC triphosphate, and/or a lower mutation rate with FTC failure than with 3TC failure.

The investigators proposed "mutational patterns, more complex than currently known, may contribute to resistance to NRTIs, including FTC/3TC."

Reference

Svicher V, Alteri C, Forbici F, et al. Different evolution and patterns of genotypic resistance profiles in emtricitabine plus tenofovir and lamivudine plus tenofovir containing regimen. XVIII International Drug Resistance Workshop. 9-13 June 2009, Fort Myers, Florida. Abstract 23.

HBV resistance to lamivudine at undetectable and low levels of viremia

Mark Mascolini for natap.org

Mutations in hepatitis B virus (HBV) reverse transcriptase conferring resistance to lamivudine arose in sizeable proportions of people with low-level viremia and even in those with undetectable HBV loads, according to results of a 64-patient study by Carlo Perno (University of Rome Tor Vergata) and collaborators at other centres.

The study involved 64 people with HBV but not HIV infection:

- In 25 people lamivudine monotherapy was failing for the first time and HBV loads ranged from 12 to 345 IU/mL (69 to 2000 copies/mL).
- Another 24 patients taking first-line lamivudine monotherapy had an HBV load below 12 IU/mL.
- Fifteen people taking first-line lamivudine plus adefovir had an HBV load below 12 IU/mL.

Perno and colleagues used phylogenetic analysis to ensure that cross-contamination or PCR errors did not distort their results.

From the first group of 25 patients with HBV viremia between 12 and 345 IU/mL, the investigators successfully sequenced HBV in 22 (88%). In the 39 people with a load below 12 IU/mL, they sequenced HBV in 10 (26%).

In the 22 people with sequenced virus and lamivudine monotherapy failing at a load between 12 and 345 IU/mL, median time on lamivudine measured 243 weeks (interquartile range [IQR] 110 to 291). Mutations could be seen in 17 of these 22 (77%), including 8 with M204V, 7 with M204I, 1 with M204I/V, and 1 with A181T. (M204 mutations in HBV are equivalent to M184 mutations in HIV.)

These primary resistance mutations arose with 1 compensatory mutation in 14% and with 2 or more compensatory mutations in the others. This finding, the investigators suggested, underscores "the existence of complex patterns of lamivudine resistance mutations even at the very early stages of virological rebound."

In 10 patients whose virus could be sequenced at a load below 12 IU/mL, Perno detected mutations in 4 (40%), the M204V mutation in 2 people, M204I in 1, and M204I plus the adefovir-related V84M in 1. Detection of mutations predicted later HBV rebound and liver enzyme flares.

Perno and coworkers recommended monitoring for HBV resistance mutations even in patients with low viremia. They believe their

findings "should be considered in setting up a rational therapeutic sequencing, potentially including pro-active switch strategies." Perno urged fellow infectious disease specialists to focus more closely on hepatitis virus research to avoid repeating errors committed in the early days of antiretroviral therapy.

Reference

Svicher V, Alteri C, Gori C, et al. Lamivudine resistance mutations in HBV reverse transcriptase can be selected even at extremely low levels of viral replication. XVIII International Drug Resistance Workshop. 9-13 June 2009, Fort Myers, Florida. Abstract 24.

TREATMENT ACCESS

FDA approval of generic ARVs

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

Drug and formulation	Manufacturer, Country	Approval date
AZT/3TC tablets 300 mg/150 mg tablets	Macleods, India	29 May 2009
3TC 150 mg and 300mg	Matrix, India	22 June 2009
Fixed dose AZT/3TC/abacavir 300 mg/150 mg/300 mg, tablets	Matrix, India	15 July 2009
Fixed dose d4T/3TC/nevirapine tablets: 40mg/150mg/200mg & 30mg/150mg/200mg	Emcure, India	16 July 2009
3TC/AZ, 30mg/60mg scored tablets, for pediatric use	Aurobindo, India	23 July 2009
AZT 60 mg scored tablets for pediatric use	Aurobindo, India	23 July 2009
Efavirenz 200mg capsules	Cipla, India	3 August 2009

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

Effective patent dates are listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

C O M M E N T

This brings the total of FDA approved generic drugs and formulations to 98 since the programme started. An updated list of generic tentative approvals is available on the FDA website:

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

Source: FDA list serve:

http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm122951.htm

ANTIRETROVIRALS

Raltegravir approved in the US for treatment-naïve patients: paranoia and anxiety added as side effects

On 8 July 2009, the US FDA granted approval for raltegravir (Isentress), to be used in treatment-naïve patients. The recommended dose for raltegravir is 400 mg twice daily, with or without food.

This expanded use in treatment-naïve patients is based on 48-week results of a randomised, double-blind trial comparing raltegravir to efavirenz, both with tenofovir+FTC backgroung nucleosides. Viral load was reduced to < 50 copies/mL in 87% of the raltegravir group compared to 82% of the efavirenz group (difference 4.7% 95% CI -1.3%, 10.6%).

Other changes were made to the US package insert included new reference to paranoia and anxiety as newly repirted side effects.

DRUG INTERACTIONS: Together with a warning about use with UGT (UDP-glucuronosyltransferases) inducers other than rifampin, specifically, "Coadministration of raltegravir with drugs that are strong inducers of UGT1A1 may result in reduced plasma concentrations of raltegravir"

SIDE EFFECTS Section 6.2: **Postmarketing experience**: the addition of paranoia and anxiety.

DRUG INTERACTIONS Section 7.1 **Effect of raltegravir on the pharmacokinetics of other agents** adds information for CYP1A2, CYP2B6 and methadone.

RESISTANCE: Treatment-naïve subjects: By Week 48 in the STARTMRK trial, the primary raltegravir resistance-associated substitutions were observed in 3 (1 with Y143R and 2 with Q148H/R) of the 6 virologic failure subjects with evaluable paired genotypic data.

Minor editorial changes were made to the patient package insert for consistency with other antiretrovirals.

The revised label will be available on the FDA web site:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
or through the National Library of Medicine's DailyMed site:
http://dailymed.nlm.nih.gov/dailymed/about.cfm
Source: FDA listserve (09 July 2009)

C O M M E N T

On 24 July 2009 the Committee for Medicinal Products for Human Use (CHMP) expressed a positive opinion on expanding the indication in Europe to patients starting HIV therapy for the first time. The positive opinion will be reviewed by the European Commission, which grants marketing authorisation to the 27 countries that are members of the European Union (EU), as well as Iceland and Norway.

Merck will need to significantly reduce the current price for raltegravir if before patients in the UK are likely to use it either as first-line treatment or as a switch option (when approved in Europe). This is particularly difficult given the potential tolerability advantages for patients have difficulties on their current regimen.

TREATMENT GUIDELINES

2009 UK (BHIVA) guidelines online for comment

The draft update of the 2009 BHIVA antiretroviral guidelines, including a review of new data presented at CROI this year, is now online and available for comment.

Sections particularly affected are:

- When to start
- What to start with
- Multiply-experienced patients and switching for toxicity

The consultation version of the addendum document can be downloaded and comments can be submitted using the form at this link:

http://www.bhiva.org/cms1224315.asp

The deadline for comments is Friday 21 August 2009.

Reference

British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. HIV Medicine 2008; 9: 563–608)

TB COINFECTION

TMC207 reduces time to sputum conversion in phase II trial on patients with drug-resistant TB

Nathan Geffen, i-Base and TAC

The results of the first of two stages of a double-blinded phase II Tibotec trial on the TB drug TMC207 have been published in the NEJM. [1]

The randomised 47 patients in South Africa, hospitalised with multi-drug-resistant TB (MDR-TB) that was resistant to isoniazid and rifampin) to receive either TMC207 (n-23) or placebo (n=24). The study was run from 5 June 2007 to 23 January 2008.

Besides standard exclusion criteria, patients resistant to aminoglycosides, other than streptomycin, and fluoroquinolones were excluded. Other exclusion criteria were previous treatment for MDR TB, neurologic or severe extrapulmonary TB, CD4 count lower than 300 cells/mm3, ART or antifungal medication or both in the previous 90 days, or significant cardiac arrhythmia.

The dosing regimen was 400 mg once daily for weeks 1 and 2, followed by 200 mg three times a week for weeks 3-8. The study drugs were provided as TMC207 100-mg tablets (or placebo) and were taken with water immediately after breakfast. The preferred background regimen for all patients was kanamycin, ofloxacin, ethionamide, pyrazinamide, and cycloserine or terizidone. The primary efficacy end point was the time to the conversion of sputum cultures from positive to negative, defined as two consecutive negative weekly cultures.

Basleine demographics included 74% male, 55% black and 87% HIV-negative. Median age was 33 (range 18-57). Three patients were excluded from the final analysis, two because they met study exclusion criteria and one because the culture test (MGIT) was negative throughout the study despite originally being smear-positive. 41 patients (20 and 21 in the TMC207 and placebo groups respectively) completed the study.

There were no significant differences in adverse events except for nausea which occured more frequently in the TMC207 arm (n=6 vs. 1; 26% vs. 4%; p=0.04). There were two grade four events, one in each arm, both considered unrelated to TMC207.

The majority of patients achieved average steady-state plasma TMC207 concentrations above the target of 600 ng per milliliter throughout the dosing period. Sputum culture conversion did not predict average steady-state plasma concentrations of TMC207.

TMC207 resulted in 11.8 times quicker conversion to sputum-negative culture (95%CI: 2.3-61.3; p=0.0003). The conversion rate to negative culture was 48% for TMC207 (10 of 21 patients) versus 9% in the placebo group (2 of 23 patients). Treatment responses were similar irrespective of trial centre and lung cavitation. Negative sputum smear (acid-fast bacilli) at week four were 57% for the placebo group and 77% for the TMC207 group. At week 8, these were 68% for the placebo group and 84% for the TMC207 group. The change from baseline in the log count of colony-forming units (CFUs) was also measured in a sub-group of 22 patients (9 TMC207 vs. 13 placebo). The median log CFU decreased to zero by week four in the TMC207 arm and week eight in the placebo arm.

Background on TMC207

In July 2003, Janssen Pharmaceutica, a subsidiary of Johnson & Johnson (J&J) filed a patent application for quinoline derivative drugs for the treatment of mycobacterial diseases including TB. The patent was published in February 2004. [2] One of these drugs, TMC207, (originally called R207910) was first described in Science in December 2004 by Andries et al [3] and was the most effective of against TB in vivo.

Andries et al. ran experiments to select TB bacteria resistant to TMC207. They then genetically sequenced these resistant strains and found that only one gene was affected on three independent strains. This gene codes a part, F0, of ATP synthase. This is a protein that uses protons to synthesise ATP from ADP. F0 is a membrane proton channel. Researchers have therefore determined that TMC207 works by inhibiting the proton pump of ATP synthase. This is a different mechanism to current anti-TB drugs and if TMC207 is effective it will not be cross-resistant with other TB drugs.

In the Andries et al. study TMC207 much higher MICs were required for laboratory efficacy against other bacteria (a subsequent study indicated activity against Buruli ulcer and leprosy in mice [5] [6]). At appropriate concentration (10 times MIC) the drug reduced bacterial load by 3 log units after 12 days. The effect was not improved with higher concentrations, suggesting, the authors say, that the effect is time-dependent rather than concentration dependent.

Another Tibotec study showed that TMC207 has in vitro activity against latent (or dormant) TB.[7] This is because dormant TB bacteria have residual ATP synthase activity.

In another phase II study 75 treatment-naïve patients with smear-positive pulmonary tuberculosis were randomised to once-daily oral TMC207 (25 mg, 100 mg, or 400 mg), 600 mg rifampin (RIF), or 300 mg isoniazid (INH) for 7 days. Significant bactericidal activity of 400 mg TMC207 was observed from day 4 onward and was similar in effect to INH and RIF over the same period. The authors concluded that TMC207 demonstrated bactericidal activity with a delayed onset and was well tolerated, and no study drug-related serious adverse events occurred. [8]

Ongoing TMC207 trials

There are five TMC207 trials registered with clinicaltrials.gov of which one is complete [9-12]. The four ongoing studies are:

- TMC207-TiDP13-C208: A phase II, placebo-controlled, double-blind, randomised trial to evaluate the anti-bacterial activity of TMC207 in subjects with newly diagnosed sputum smear-positive pulmonary infection with MDR-TB. This is the second stage of the study discussed in this summary and is currently recruiting patients including in six South African hospitals. 24 week treatment period for 150 patients with 96 week follow-up. Estimated completion May 2011.
- TMC207-TiDP13-C110: A phase I study to examine, in 16 healthy volunteers, the interactions between TMC207 and lopinavir/ritonavir. Recruitment has not begun.
- TMC207-TiDP13-C117: A phase I study in 16 HIV-positive people to examine the interactions between TMC and nevirapine. Recruitment has not begun.
- TMC207-TiDP13-C209: A phase II, open-Label trial with TMC207 as part of an MDR-TB treatment regimen in 225 patients with sputum smear-positive pulmonary infection with MDR-TB. The estimated study completion date is June 2012. Recruitment has not begun.

C O M M E N T

TMC207 is the most promising of several new TB drugs that are in development, especially since it has in vitro activity against dormant TB.

Even though the need for new TB drugs is at least as great as for ARVs, registration is unlikely to be before 2011, even if the Phase 3 studies show efficacy and good safety.

Compassionate access for TMC207 should be made available for patients with XDR-TB.

References

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10. NIH TMC207-TiDP13-C110: Interaction study in healthy volunteers with lopinavir/ritonavir. http://clinicaltrials.gov/ct2/show/NCT00828529
11. NIH TMC207-TiDP13-C117: Interaction study in HIV-1 infected patients with nevirapine (NVP). http://clinicaltrials.gov/ct2/show/NCT00910806
12. NIH TMC207-TiDP13-C209: Trial to evaluate the safety, tolerability, and efficacy of TMC207 as part of an individualised MDR-TB treatment regimen in patients with sputum smear-positive pulmonary MDR-TB.

http://clinicaltrials.gov/ct2/show/NCT00910871

BASIC SCIENCE

Recent basic science updates from Richard Jefferys excellent web log.

Maximum suppression: ART intensification does not reduce residual viral load

Richard Jefferys, TAG

One of the most controversial questions in the field of HIV research is whether current antiretroviral therapy (ART) combinations maximally suppress viral replication. New technologies have allowed researchers to detect down to just 1 copy of HIV RNA per mL of blood and, even when the viral load is undetectable on commercially available tests (which typically can only detect 50 copies or more), most people on ART have a few copies of HIV RNA detectable in their samples. These HIV RNA copies could either be the product of ongoing rounds of viral replication (in which infected cells release new viruses that go on to infect other cells), or alternatively they could be produced by long-lived chronically infected cells. In the latter scenario, ART would prevent the newly-produced virus from being able to infect any other cells, but the drugs would not be able to eliminate the chronically infected cell.

Over the past few years, scientists have debated – often quite heatedly – which of these possibilities is true. Recent evidence has generally favored the view that, in most cases, ART is maximally suppressing HIV replication; for example, a study of viral evolution in people undergoing intermittent ART interruption found no evidence of ongoing viral evolution during the periods when participants were on therapy.

A study just published in PNAS tackles the question another way, by investigating whether intensifying ART by adding new drugs has an effect on residual viral load. [1]

Out of 15 total participants, only 9 consistently showed HIV RNA levels above 1 copy/mL prior to ART intensification (median 3 copies/mL). The highest level detected was around 30 copies/mL. The researchers found that ART intensification had no effect on these residual viral levels, indicating a lack of ongoing HIV replication. The results add to the evidence that low-level HIV RNA detectable in people on ART does not derive from ongoing viral replication, but rather a stable reservoir of infected cells. The major implication is that, in order to cure HIV infection, new strategies are needed to identify and eliminate this reservoir. PNAS has designated the paper “Open Access,” click on the title link for the PDF.

References:

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http://www.pnas.org/content/early/2009/05/22/0903107106.full.pdf+html

The role of Ad5-specific CD4 T-cells in enhancing risk of HIV acquisition in the Merck vaccine trial

Richard Jefferys, TAG

In September 2007 it was announced that immunizations were being halted in the STEP study, a phase IIb efficacy trial of Merck’s HIV vaccine candidate. A review of the interim results by the Data Safety Monitoring Board found that there was no possibility of the vaccine showing efficacy for preventing HIV infection, or reducing post-infection viral load levels in vaccine recipients who became infected. These events and the subsequent fallout were covered in grisly detail on this blog.

The most surprising and disturbing finding from STEP was that receipt of the vaccine was associated with a significantly increased risk of HIV acquisition in a subset of trial participants: uncircumcised men with pre-existing antibodies against adenovirus serotype 5 (Ad5). The Merck vaccine construct used an attenuated Ad5 virus vector as a delivery vehicle for the HIV antigens Gag, Pol & Nef. In its natural form, Ad5 causes severe colds and many people are exposed during childhood and hence have anti-Ad5 immune responses.

When the data from STEP showing enhanced risk of acquisition became known, there was understandably much discussion of what the potential mechanism might be. One hypothesis posited that the presence of anti-Ad5 antibodies at baseline was a marker for the presence of Ad5-specific CD4 T cell responses, and immunization with the Ad5 vector activated Ad5-specific CD4 T cell responses, thereby increasing the number of potential target cells for HIV infection in vaccine recipients. This hypothesis was explored to limited extent in one of the papers presenting the STEP results that was published in The Lancet last year by Juliana McElrath and colleagues; in that paper, analyses of Ad5-specific CD4 T cells showed that responses tended to be lower in vaccine recipients who became HIV infected, at least in peripheral blood.

Two new studies just published online in Nature Medicine now offer a more detailed absolution of Ad5-specific CD4 T cells. [1]

The results show that baseline antibody titres did not correlate with the magnitude of the Ad5-specific CD4 T cell response (as

measured by production of IL-2, interferon gamma, TNF-alpha, MIP-1beta and perforin - Th2-type cytokine production by Ad5-specific CD4 T cells has not yet been evaluated). Furthermore, most individuals who lacked anti-Ad5 antibodies nevertheless displayed Ad5-specific CD4 T cell responses. The studies also demonstrate that receipt of the vaccine rapidly induced both Ad5-specific CD4 T cells and antibodies in people who lacked them at baseline, suggesting that if these responses enhanced the risk of HIV infection then the enhancement should have been seen in all vaccine recipients after the initial immunisations, not just the subset with detectable anti-Ad5 antibodies at baseline.

While these papers make an important contribution to the analyses of what occurred in STEP, there are some caveats. Most critically – and contrary to what has been written in one media story on The Scientist website [2] – the new results do not absolve the Merck HIV vaccine of significantly enhancing the risk of HIV acquisition among uncircumcised men with pre-existing antibodies against Ad5. It is disheartening to read quotes from Alan Bernstein, Executive Director of the Global HIV/AIDS Vaccine Enterprise, erroneously stating otherwise. Also in The Scientist article, Nelson Michael is quoted as saying that including circumcision status as a variable in the multivariate analyses of STEP "washes out" the enhancing effect of vaccination. Based on Susan Buchbinder's talk at Keystone earlier this year, this is simply not true; what the circumcision data show is that the enhancement effect was most significant in the uncircumcised subgroup with anti-Ad5 antibodies. Additionally, Buchbinder noted that continued follow-up of STEP participants indicates the enhancement effect has waned over time, which adds to the evidence that receipt of the Ad5 vector was responsible.

Another more speculative caveat is that the new data may not entirely rule out a role for Ad5-specific CD4 T cell responses in the trial outcome. One possibility that remains to be studied is whether the presence of persistent Ad5 infection alters the behaviour of Ad5-specific CD4 T cell responses after immunization (i.e. if natural Ad5 antigens are being expressed somewhere in the body, Ad5-specific CD4 T cells would be expected to traffic to those sites). Recent research from Linda Gooding's group at Emory (abstracts and links appended at the end of the post) has employed PCR to confirm that Ad5 infection can persist in humans. The main cell type infected by Ad5 in these studies was T cells, and activation of infected T cells stimulated Ad5 replication. In the context of the STEP results, these data suggest several questions:

- Can persistent Ad5 infection be detected in the foreskin?
- Is there any correlation between Ad5 serostatus and detection of persistent Ad5 infection?
- Does immunisation with an Ad5 vector lead to any detectable changes in the interactions between Ad5-specific CD4 T cells and Ad5-infected cells?

Juliana McElrath's Lancet paper cites the need to consider events in the mucosa, stating that Ad5-specific CD4 T cells "could have trafficked to mucosal sites—a process known to occur in natural infection—and thus increased the number of susceptible CD4+ T-cell targets for HIV… To address this possibility, studies are planned to examine lower gastrointestinal tissue and foreskin after immunization for enhanced T-cell activation." This idea is not unprecedented, as studies from Larry Corey's laboratory have strongly implicated the persistent presence of activated HSV-2-specific CD4 T cells interacting with HSV-2-infected cells in the mucosa as the explanation for the association between HSV-2 infection and increased susceptibility to HIV acquisition. At the Keystone conference earlier this year, Corey showed that these interactions continue to be detectable even when HSV-2-infected individuals are on chronic suppressive therapy with acyclovir, offering a reason for the failure of the drug to reduce the risk of HIV infection in several large trials.

There is one other slightly uncomfortable caveat to the Nature Medicine papers: both groups of researchers include people working on vaccines using alternative adenovirus serotypes. If evidence did suggest that Ad5-specific CD4 T cells played a role in enhancing risk of HIV acquisition in STEP, this could potentially impact their work because Ad5-specific T cell responses have been shown to cross-react with multiple adenovirus serotypes. Because the alternative adenovirus-based vaccines are being developed for neglected diseases that do not represent profitable vaccine markets, it's not a case of suspecting significant financial conflicts-of-interest, but the issue should perhaps have been acknowledged in the papers.

Source: TAG basic science project (22 Jul 2009).
http://tagbasicscienceproject.typepad.com
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Tracing HIV reservoirs

Richard Jefferys, TAG

Two new papers offer differing perspectives on the reservoirs of HIV that persist despite effective antiretroviral therapy.

Nicolas Chomont and colleagues demonstrate that when memory CD4 T cells containing integrated HIV proliferate (as most memory CD4 T cells do occasionally in a process known as homeostatic self-renewal), they copy the HIV provirus along with their own genomes. [1]

When CD4 T cell numbers decline, homeostatic proliferation occurs more frequently and Chomont's paper shows that this is associated with an increase in the number of latently infected memory CD4 T cells. The researchers describe the cells that undergo more frequent proliferation in this setting as "transitional memory" T cells. At earlier stages of infection when the CD4 T cell pool is relatively intact, the reservoir of infected memory CD4 T cells is found to be far smaller and integrated virus is primarily located in "central memory" cells that divide less frequently.

Based on these findings, the study authors suggest that anticancer drugs that interfere with memory T cell proliferation should be studied for their potential to deplete the HIV reservoir. However, given the potential toxicities associated with inhibiting T cell proliferation, the risk/benefit of such trials would need to be carefully evaluated. A more ideal therapy would be one that only targeted dividing CD4 T cells containing HIV DNA, but it is currently unclear whether such an approach is within the realm of possibility.

The second paper - by Timothy Brennan and colleagues from Bob Siliciano's laboratory - uses genetic analyses of HIV sequences to show that there is a reservoir of virus that seems to be coming from a cell type other than memory CD4 T cells. [2]

The study finds that in most cases, the residual virus detectable in individuals on suppressive ART is genetically distinct from the virus found in memory CD4 T cells. The authors note in their conclusion: "Numerous laboratories are actively pursuing various eradication strategies, most of which involve some aspect of targeting and purging the latent reservoir in resting memory CD4+ T cells. If much of the residual viremia of patients undergoing HAART comes from another reservoir or compartment as suggested here, then eradication strategies will have to include ways to target and purge this additional reservoir to be successful."

Source: TAG basic science project (24 Jun 2009).

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Illuminating early events in HIV infection using single genome amplification

Richard Jefferys, TAG

Two papers in the current Journal of Experimental Medicine offer unprecedented insight into the initial interactions between virus and host after HIV infection. An accompanying commentary by Zabrina Brumme and Bruce Walker eloquently articulates what these studies have achieved: "By identifying persons before seroconversion, pinpointing the transmitted virus, and assessing immune responses to that particular variant as it evolves, they provide a novel view of host and viral dynamics during the earliest stages of infection." [1]

In both studies the researchers use an optimised version of a technique called Single Genome Amplification (SGA), originally developed by Sarah Palmer and colleagues at the National Cancer Institute. While costly and labour-intensive, this technique allows sequencing of the HIV genome without many of the potential confounding errors that can occur with standard PCR. The researchers also used the sequences obtained by SGA to synthesise peptides for CD8 T cell response assays; this allowed detailed tracking of the impact of CD8 T cell responses on the virus genome.

The study results echo prior work from these groups suggesting that most HIV transmission events involve a single isolate; in 11 out of 12 cases SGA showed that all detected sequences were related to a single infecting virus. The remaining individual was infected with two viruses that could be unambiguously identified based on their sequences. In terms of viral evolution after infection, the researchers found that between transmission and peak viraemia, diversification of HIV sequences was essentially random and showed no evidence of selection pressure from host immune responses. Subsequently, between 9-16 days later, the effects of selection became obvious, particularly effects attributable to HIV-specific CD8 T cell responses. By 32-45 days postinfection, almost the entire replicating virus population in each subject studied was replaced by viruses with mutations at two to five distinct loci in the genome, evincing selection pressure from both CD8 T cell and neutralizing antibody responses (and other unidentified sources also, perhaps innate and/or CD4 T cell immune responses).

The level of detail involved in the study also allowed the researchers to document virus escape from CD8 T cell responses earlier than has previously been reported. Mathematical modelling of the data indicated that HIV-specific CD8 T cells are more efficient at killing virus-infected cells during acute infection than prior estimates have suggested. Discussing the implications of their findings for T-cell-based vaccines, the authors state: "Modelling implied that a single T cell response was contributing as much as 15–35% of viral decline with multiple T cell responses. The implication of these observations is that vaccine-induced HIV-1–specific T cells will contribute to control of acute viraemia if they are activated early in subsequent HIV-1 infection. However, because of the very rapid escape that occurs within the first few weeks of infection, T cell vaccines will need to stimulate a considerable breadth of T cell responses, clearly greater than the median of three epitopes induced by the Merck vaccine."

Source: TAG basic science project (22 Jun 2009).

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FUTURE MEETINGS

2009 conference listing

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.

11 September 2009: Clinical Pharmacology of Tuberculosis Drugs, San Francisco

http://www.virology-education.com

12-15 September 2009: 49th ICAAC, San Francisco

http://www.asm.org

29 October-1 November 2009: 47th IDSA, Philadelphia.

http://www.idsociety.org

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

http://www.i-Base.info

All i-Base publications are available online, including editions of the treatment guides. The site gives details about i-Base, the UK Community Advisory Board (UK-CAB), our phone service and meetings, as well as access to our archives and an extensive range of links. It can be used to order publications and regular subscriptions to be delivered by post or email (as PDF files).

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

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

RSS news feed has been introduced for HIV Treatment Bulletin for web and PDA access - we welcome your feedback on this new way to provide treatment updates.

A section on Education, Advocacy and Training includes our training manual for advocates with eight 2-hour modules that include questions and evaluation. Training modules start with basics, including CD4, viral load and other monitoring tests, combination therapy and side effects, and include overviews of the main opportunistic infections. There is a module on pregnancy and another module on IV drug users and treatment.

An average of 6000 pages are served from the site each day.

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To subscribe please fill out the form at this link:
http://www.i-base.info/forms/newssub.html

Training manual – revised, updated and now fully online

This established training resource has been revised and updated and is now online in new format.

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

The Training Manual for Advocates provides entry-level curriculum relating to HIV and treatment.

It is made up of 8 modules for learning about aspects of HIV care has been updated and published online as an interactive resource. It provides entry-level curriculum relating to HIV and treatment.

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

http://www.i-base.info/manual/en/index.html

Sections include:

1. Immune system and CD4 count
2. Virology, HIV and viral load
3. Introduction to antiretrovirals (ARVs)
4. Side effects of ARVs
5. Opportunistic infections and coinfections
6. HIV and pregnancy
7. Drug users and HIV
8. Clinical trial design and the role of advocates

Each module includes learning objectives, non-technical review material, test questions, an evaluation and a glossary.

We hope this will be useful for training advocates and other related healthcare workers as well as for HIV-positive people who want to know more about aspects of their healthcare.

The training manual was previously only available online as a PDF document and has been widely translated. Earlier editions are available in Russian, Portuguese, Hindi and Nepalese as are available as PDF files.

Generic clinic forms

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

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

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

Please contact the i-Base office if you would like help adding your own hospital or Trust logo to these forms.

Report assessing the treatment information needs African people in the UK living with HIV

This report by Winnie Sseruma and i-Base includes an analysis from workshops held last year and details African use and experience of current treatment information resources.

http://www.i-base.info/pdf/africantreatmentneeds.pdf

i-Base Book: “Why we must provide HIV treatment information”

Photography by Wolfgang Tillmans

i-Base has worked as a treatment literacy project for over six years. Over this time we have always produced copyright-free material and encouraged other organisations to use, translate and adapt our material. Through this work, we have been very lucky to develop links to many other advocacy projects outside the UK.

A recent meeting, held in Cape Town earlier this year, focused on how to raise the profile of treatment literacy. One result from the meeting is a publication “Why we must provide HIV treatment information”.

With text provided by activists from 25 countries and 50 full colour photographs by Wolfgang Tillmans, this limited edition 100-page publication is being sold by i-Base to raise funds to help support our international treatment literacy projects.

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community treatment workers across the UK that has been meeting for three years. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

The CAB has a separate website, where reading material, reports and presentations from these meetings are posted.

http://www.ukcab.net

World CAB - reports on international drug pricing

Two reports from meetings between community advocates and pharmaceutical companies, that focused on pricing issues and global access to treatment, and that are now available online.

Both are available to download as a PDF file from the i-Base website.

http://www.i-base.info/wcab/index.html

Introduction to combination therapy

June 2008 edition

This non-technical patient guide to treatment explains combination therapy, how well it works, who can benefit from it, when to start taking it, some differences between treating men and women, side effects, the best combinations, changing treatment, taking part in drug trials, your relationship with your doctor, the importance of adherence, and how to avoid drug resistance.

Printed and/or PDF versions of earlier versions of this booklet are available in other languages.

Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support

March 2009 edition

This is a new i-Base guide. It is a non-technical patient guide to Hepatitis C and coinfection with HIV.

This booklet mainly covers treatment related aspects of coinfection including transmission, natural history, tests and monitoring, HCV treatment and side effects, research into new drugs and living with coinfection. It also includes contributions from a wide range of people with direct experience of coinfection. The online version of this guide includes additional text.

Guide to changing treatment: what to do when your treatment fails

September 2008 edition

This is a non-technical patient guide to changing treatment, drug resistance and what to do if treatment fails. It is updated to include recent advances in new treatments and strategies, especially in relation to use of new and expanded access treatments.

This booklet helps patients in discussions with doctors, and covers what can be done if viral load starts to rise, and the importance of considering or finding out why the current combination failed, treatment strategies and new pipeline treatments.

Guide to HIV, pregnancy & women's health

January 2009 edition

Updated and revised, this patient guide helps women get the most out of HIV treatment and care before, during and after pregnancy. It should help whether on therapy or not and includes information for the mothers health and for the health of the baby.

The guide gives information on medication, Caesarean section and breastfeeding, as well as details of other sources of help. It is aimed at people in a wide range of circumstances including positive women thinking about having children and pregnant women who have recently been diagnosed HIV-positive.

Guide to avoiding & managing side effects

May 2008 edition

This is a comprehensive 72-page A5 guide that is aimed at helping anyone using HIV drugs to get the most out of their treatment, the most out of their relationships with their doctor and other health professionals, to get better medical care to improve their health and, most importantly, to enjoy a better quality of life.

Translations of i-Base guides

Original material published by i-Base can be translated and reprinted, and has so far been produced in over 35 languages.

More information about this process is available on the i-Base website.

In addition, PDF files of some of the translated publications are available on the i-Base site.

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

http://www.i-base.info/about/downloads.html
Languages currently include:

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

Treatment 'Passports'

These popular booklets are for HIV-positive people - whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Like all i-Base publications, they are available free as single copies, or in bulk.

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 10 times a year in a printed version, in a pdf file that we can email to you, and on our website.

The printed version is available at most HIV clinics in the UK and is available free by post.

HTB South

A quarterly bulletin based on HTB 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.

Treatment information request service - 0808 800 6013

i-Base offers specialised treatment information for individuals, based on the latest research.

We can provide information and advice over the phone, and we can mail or email copies of the latest research studies relevant to the caller.

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

Online Q&A service

An online 'question and answer' service that now has over 800 questions online. Questions can either be answered privately, or if you give permission, we will post the answers online (omitting any personally identifying information).

http://www.i-base.info/questions
Recent questions include:

- Worried about facial lipoatrophy, what shall I do?
- Is it OK to take probiotic cultures with HIV meds?
- Is d4T+3TC+EFV good enough?
- Can I take these supplements with my HIV treatment?
- Can I use Zyban to stop smoking if I'm on HIV treatment?
- Could Hunt's syndrome have affected my CD4 count?
- What would happen if somebody starts with a CD4 count of zero and on entry inhibitor?

- What can I replace Atripla with?
- Is it safe for a man to give oral sex to a woman?
- I am feeling tired, what shall I do?
- Can this person receive free treatment in the UK?
- Do I have a natural resistance to HIV?
- Can I use terbinafine?
- Is it safe to take milk thistle supplements when on Atripla?
- Questions about HIV and swine flu in the UK
- Can I fast?
- Is this AIDS dementia?
- Could you explain my results and opportunistic infections?
- Can I use minoxidil 5% scalp solution if I'm on HIV treatment?
- Could melanotan injections have stopped my ARVs from working?
- Do melanotan injetions interfere with my ARVs?
- Will Immunoxel and dermavir patches be available in the UK?
- Switching back to Kaletra after efavirenz…
- How to remove genital warts?
- Is it OK to use muscle gain powder?
- Do we have to start using condoms?

Find HTB on AEGiS

AEGiS.org - the longest established and largest global resource of online HIV information - includes HTB in the regular journals that it puts online. You can find us at:

http://www.aegis.org/pubs/i-base/2009

The AEGiS daily email news service also carries i-Base conference reports.

Order i-Base publications via the internet, post or fax

People with internet access can use our website to order and receive publications. You can access our publications online or subscribe to receive them by email or by post; and you can order single copies or bulk deliveries by using the forms at:

http//www.i-base.info/forms/index.html

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

h-tb

HIV Treatment Bulletin

HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website: http://www.i-Base.info; by fax or post using the form on the back page 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 i-Base

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

However, any donation that your organisation can make towards our costs is greatly appreciated.

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(Our bank details for donations: NatWest, Kings Cross Branch, 266 Pentonville Road, London N1 9NA, Sort Code 60-12-14. Account Number: 28007042)

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I do not wish to make a regular donation but enclose a one-off cheque in the sum of _____ instead.

I wish to make a one of donation (minimum £12.50 inc p&p) for the Treatment Literacy Photogrpahy Book £ _____.

GIVE AS YOU EARN

If your employer operates a Give-As-You-Earn scheme please consider giving to I-Base under this scheme. Our Give-As-You-Earn registration number is **000455013**. Our Charity registration number is 1081905

Since many employers match their employees donations a donation through Give-As-You-Earn could double your contribution. For more information on Give-As-You-Earn visit www.giveasyouearn.org

REFUNDS FROM THE TAX MAN

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

Whichever of the above schemes you might chose to donate to i-Base we would like to thank you very much for your support.

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

1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ 100 ☐ Other _____ _____

Guide To HIV, Pregnancy and Women's Health *(January 2009)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

NEW: Introduction to Combination Therapy *(June 2008)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

Changing Treatment - Guide to Second-line and Salvage Therapy *(September 2008)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

Guide To Avoiding and Managing Side Effects *(May 2008)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

Guide To HIV and hepatitis C coinfection *(May 2007)*

1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **100** ☐ **Other** _____ _____

Translations of earlier treatment guides into other languages are available as PDF files on our website

Phoneline support material *(pls specify required number of each)*

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

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

1 Sheet ☐ **1 pad** ☐ **5 pads** ☐ **10 pads** ☐ **Other** ☐ _____ _____

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