

## In this issue

Iron deficiency .....	p. 1
NNT for lipid lowering .....	p. 3
House dust mites and how to get rid of them.....	p. 4
HIV-1 virus: finding it and stopping it.....	p. 5
King's Fund conference on the cities .....	p. 8

*The views expressed in **Bandolier** are those of the authors, and are not necessarily those of the NHSE Anglia & Oxford*

## Just like that

Or so it seems when it comes to HIV infection. For those of us not in the front line, it seems just a bit miraculous that new treatments and tests can come along in combination to empty wards and slash death rates in a disease that seemed hopeless. Wonderful though new developments like this are, their speed poses problems for purchasers and providers. This month *Bandolier* gives a flavour of the new developments.

## Under the fez

We duck the issue of cost effectiveness in the NHS and society - keep it under the fez, so to speak. But then *Bandolier* is not alone, because everyone else is ducking it too. This is another one of those areas where a bit of foresight with some expertise ought to provide some back-of-envelope estimates of impact to inform policy. While imprecise, it is an approach that would take much stress out of the lives of those infected with HIV and their carers, and because of the way HIV treatments are funded, not so difficult, really.

## Get a new putter

While on cost effectiveness, *Bandolier* was struck by an advert in the journal *Urology*. It extolled the virtue of some lower cost treatment for some prostate condition - so that with the savings a patient made, he could get a new putter! *Bandolier* can't even get onto the golf course.

## Bandolier conferences

*Bandolier* is working hard to get more conferences on the road. By the next issue you should have a list of those topics to be covered in 1997/8 - but we always welcome your suggestions. For now you might want to pencil in a date in late September or early October for a one-day conference on Chlamydia infection. For early notification fax Eileen on 01865 226978.

## IRON DEFICIENCY

*Bandolier* was struck by an article in *JAMA* on the prevalence of iron deficiency in the USA, which hit its desk at the same time as a report called *The Hunger Within* on child poverty and nutrition in the UK. Naively, *Bandolier* thought that iron deficiency was of only historical interest in Britain, though important in developing countries with poor diets. Wrong again, apparently.

## Iron deficiency in the USA

The US study [1] was conducted on just under 25,000 people aged one year or more as part of an ongoing health and nutrition survey. This collects data in household interviews and standard physical examinations in mobile examination centres. Biochemical information was available on 79% of the interviewed sample. Iron deficiency was defined as two or more abnormal results for free erythrocyte protoporphyrin, transferrin saturation or serum ferritin. Iron deficiency anaemia was defined as iron deficiency plus a low haemoglobin.

## Results

- For children (ages 1 to 11 years), 9% of those aged 1 to 2 years were iron deficient, and 3% had iron deficiency anaemia.
- For women of all ages the figures were 5 to 11% and 2 to 5% respectively.
- Only men aged 50 years or more had significant rates of 2 to 4% and 1 to 2% respectively.

## And the UK?

*The Hunger Within* [2] pointed out that iron deficiency and low haemoglobin in children has been shown to be common in the UK. Two papers were impressive [3,4].

## BANDOLIER 2ND ANNUAL

The second *Bandolier* volume of collected issues (21 - 34) is available by sending a cheque for £14. (£18 overseas), made out to **Oxfordshire Health**, to:

Mrs Eileen Neail  
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We cannot chase paper, so don't ask us to send invoices. The only way you can get this limited edition collector's item is to send a cheque with your order.

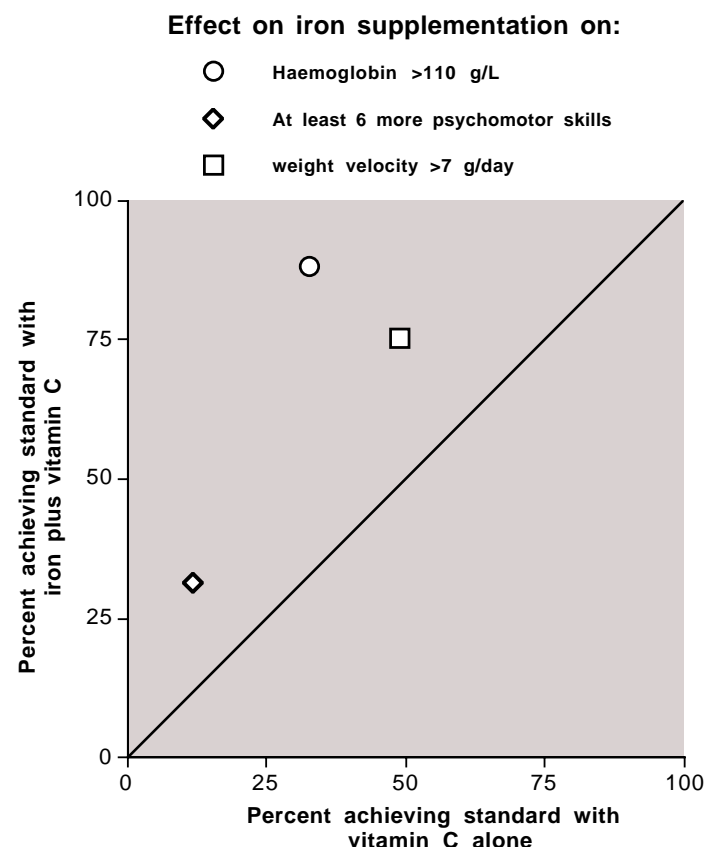
The first of these [3] was a randomised trial of iron supplementation in children aged 17 to 19 months in Birmingham. Parents of every child in this age group in four health centres in central Birmingham were sent an invitation to attend for routine surveillance, including a haemoglobin estimation. Four hundred and seventy children attended. Of these, eight (2%) had haemoglobin levels below 80 g/L, and were treated immediately. A further 116 (25%) had haemoglobin values of 80 to 110 g/L, and were invited to attend an anaemia clinic.

In the clinic further clinical investigation was done, and eventually 110 children were randomised to iron 24 mg plus vitamin C 10 mg daily, or an identical vitamin C preparation, for two months. Assessments before and after included physical measures (height, weight), psychomotor development, and haemoglobin and other biochemical variables.

## Results

Iron supplementation over two months, compared with no iron supplementation, resulted in significant improvements. The number of children with a haemoglobin of at least 110 g/L was larger, with a number needed to treat (NNT) of 1.8 (1.4 to 2.6). The number of children increasing their psychomotor skills by six points (the average over this period in this age group) increased, with a NNT of 5.3 (2.9 - 33). The number of children whose weight velocity was 7 grams per day or above (the average for this age group) increased, with a NNT of 3.8 (3.2 to 14).

This beautifully presented paper puts these results into perspective, and summarises four previous studies of iron supplementation on psychomotor development in children. All involved small numbers of children, but results of iron supplementation were impressive in three of them. A systematic review of all these trials would make interesting reading.



## How to do it

*Bandolier* is always attracted to papers which have the word implementation in their title. A study from Bristol [4] reported results from screening children aged 13 to 24 months, two years apart. The incidence of low haemoglobin (less than 105 g/L) in the first screen was 25%. After a combined approach by midwives, health visitors, treatment room nurses and the primary health care team to improve dietary advice, screening a similar cohort two years later reduced the incidence of low haemoglobin to 8%.

What was interesting was the simple way in which the haemoglobin screening had been included in an immunisation programme for measles, or measles, mumps and rubella. The uptake of immunisation was 93%, and that of screening 90%.

## Comment

This paper is a nice example of a problem, with an effective treatment, and a way of doing it. But the authors themselves point out that by measuring haemoglobin and mean corpuscular volume they may be missing part of the problem.

Iron metabolism is a complicated business. Before frank anaemia develops with low haemoglobin, iron deficiency will occur, which may have problems of its own. How to measure iron deficiency is itself questioned, and it has been suggested that the US studies [1] may underestimate it.

In a closely argued but compelling study, a Swedish group [5] suggested using a serum ferritin cut-off of 16 µg/L. They found that 40% of 15-16 year old girls and 15% of boys were iron deficient, which is not out of line with studies in other countries.

Why should this be? Well, we lead low energy lives, and have a reduced food intake and different dietary balance from our ancestors. So we have less iron intake, and it may be less well absorbed. *Bandolier* would like to see a comprehensive review. Is there one we have missed?

### References:

- 1 AC Looker, PR Dallman, MD Carroll, EW Gunter, CL Johnson. Prevalence of iron deficiency in the United States. *Journal of the American Medical Association* 1997 277: 973-6.
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- 4 J James, P Lawson, P Male, A Oakhill. Preventing iron deficiency in preschool children by implementing an educational and screening programme in an inner city practice. *British Medical Journal* 1989 299: 838-40.
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# NNTs FOR LIPID LOWERING

*Bandolier* was delighted to find that someone had got to grips with lipid lowering trials in primary and secondary prevention and pulled all the data together in a systematic review [1]. Even better was that results were presented as numbers-needed-to-treat (NNT).

## Review

The review sought studies of primary, secondary, and tertiary prevention identified from electronic searching and reviews up to the end of 1995. Included studies were randomised and involved standard antidyslipidaemic therapy (diet, pharmaceuticals or surgery). All studies were single-blind, and most were double-blind.

## Results

The main results are shown in the table for several different end-points, and in the graph for myocardial infarction (MI) or cerebrovascular (CV) death.

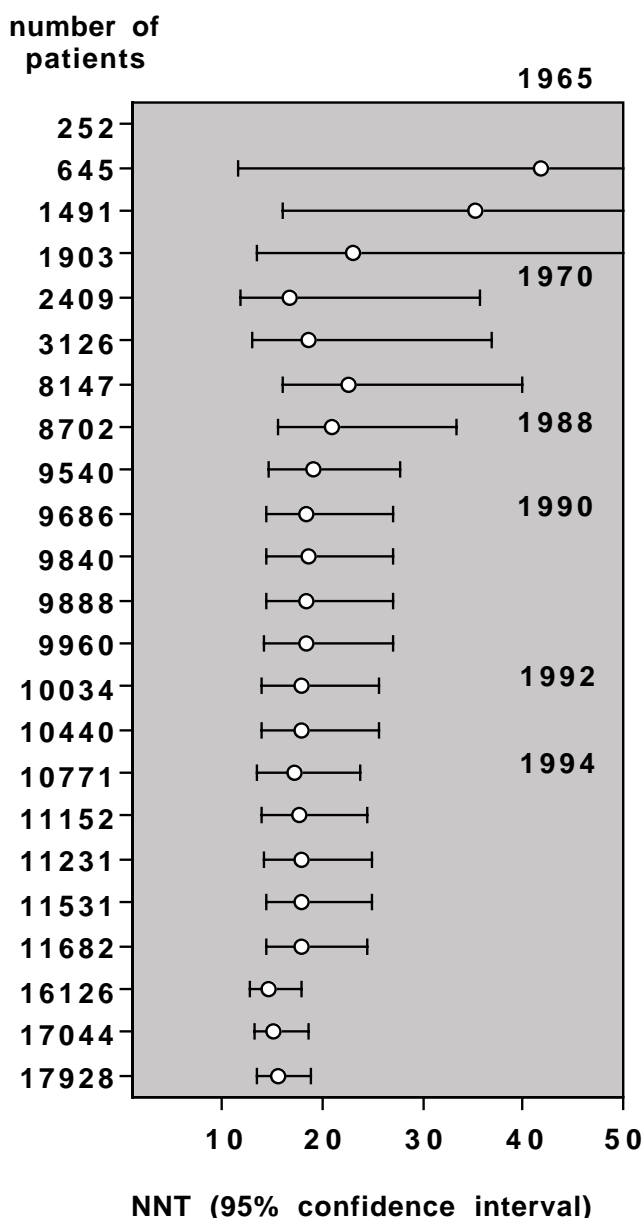
### Primary prevention (no previous heart attack)

In seven primary prevention trials with 29,683 subjects, active treatment resulted in an average reduction of cholesterol of 13%, compared to an increase of 1% in the controls over an average duration of 4.9 years. This gave a NNT for death from heart attack or stroke of 69 (54 to 99). That is, 69 people have to have lipid lowering therapy for five years to prevent one of them dying from heart attack or stroke.

### Secondary prevention

In 25 secondary or tertiary prevention trials with 18,452 subjects, active treatment resulted in an average reduction of cholesterol of 18%, compared to no change in the controls over an average duration of 4.9 years. This gave a NNT for death from heart attack or stroke of 16 (13 to 19). That is, 16 people have to have lipid lowering therapy for five years to prevent one of them dying from heart attack or stroke. These results were similar in the newer studies, those involving diet only, niacin, or coenzyme A reductase inhibitors.

Cumulative NNT for MI and/or CV death in secondary and tertiary lipid lowering prevention trials



Prevention studies	Number of trials	Number of subjects	Number-needed-to-treat			
			MI or CV death	MI	CV death	All deaths
<b>Primary prevention</b>						
All trials	7	29,683	69 (54 - 99)	78 (60 - 121)	347 (209 - 1981)	931 (212 - no benefit)
<b>Secondary prevention</b>						
All trials	25	18,452	16 (13 - 19)	28 (23 - 36)	33 (26 - 50)	37 (26 - 67)
Newer studies	13	8,390	15 (13 - 19)	23 (18 - 32)	53 (41 - 84)	41 (31 - 66)
Diet only	7	2,407	15 (11 - 29)	42 (23 - no benefit)	25 (16 - 72)	29 (15 - no benefit)
Niacin	5	4,835	15 (11 - 30)	38 (21 - no benefit)	32 (16 - no benefit)	28 (16 - no benefit)
HMG-CoA reductase inhibitors	9	7,934	15 (13 - 19)	23 (18 - 31)	44 (34 - 67)	37 (28 - 58)

## Comment

This is an interesting paper, and worthwhile having in the filing cabinet. Some cautionary notes, though, since the figures in the tables do not always add up, and there is a conceptual flaw in the way in which negative NNTs (that is, those where control is better than treatment) are handled.

However, the way in which the benefits of treatment are handled cumulatively is illuminating. The early trials included some which did not have big effects (perhaps because they were small). The first trial in 1965 showed no benefit, and doesn't even appear on the graph because of that. If that was assumed to be the truth, then the benefits of lipid lowering would not have been discovered. As it was the NNTs settled down to about 15 by the time about 9,000 patients had been studied in 1988. *Bandolier* keeps seeing examples where the results of single, small trials can over-or under-estimate benefits of an intervention.

Reference:

- 1 CM Rembold. Number-needed-to-treat analysis of the prevention of myocardial infarction and death by antidiabetic therapy. *Journal of Family Practice* 1996 42: 577-86.

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## OLD CURIOSITY SHOP

House dust mites have been recognised as a major source of allergen. Because we have wall-to-wall carpets, soft furnishings, and central heating in most homes, the density of house dust mites (*Dermatophagoides pteronyssinus*) in our homes has increased dramatically. Over 80% of young adults and children with asthma are hypersensitive to its allergens.

### The house dust mite is common

The concentration of the main allergen protein, Der p1, can outlast the mite itself, because it is found in high concentrations in mite faeces. In 1991, 40 houses in south Manchester were studied for concentrations of the Der p1 allergen [1], in dust collected from bedroom and living room carpet, and from mattresses. Concentrations varied widely between houses, without much variation with season. Concentrations in dust taken from mattresses and carpets were in the range of about 0.5 to 200 µg/gram of dust.

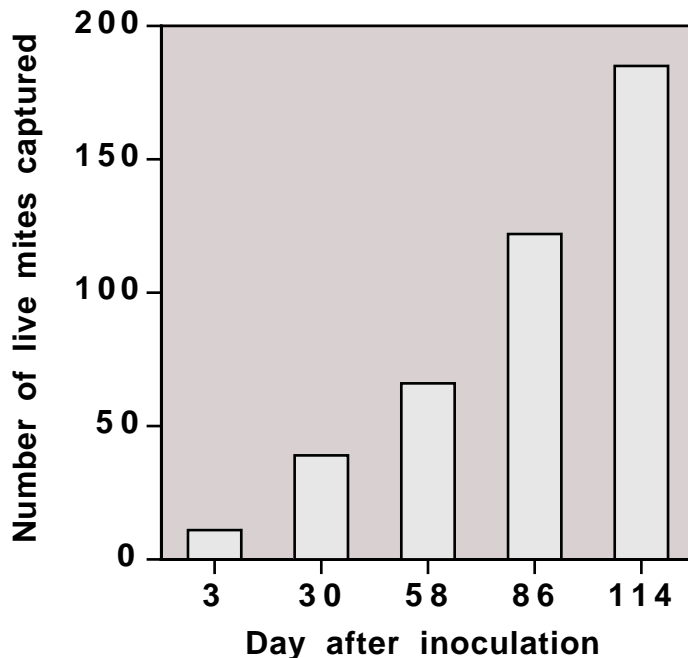
### Getting rid of the mites

A number of methods has been tried, including using acaricides (mite-killing chemicals) and liquid nitrogen (the mites are killed by freezing). The problem is that these methods may kill the mites, but the Der p1 allergen that has collected is still there.

Another approach is steam cleaning. A classic paper [2] did experimental work in the laboratory, and in the field. In the laboratory, carpet squares were seeded with live mites. Some were cleaned immediately with a domestic steam cleaner, but whether cleaned or not all the carpet squares were incubated in conditions of temperature and humidity, and with food that the mites find congenial.

Over a period of 114 days the number of live mites was sampled from the squares. You do this by heating the bottom of the square and catching mites on sticky tape as they climb up to get away from the heat. Results were that only one square originally steam cleaned showed any growth, while the mites thrived in the uncleaned squares.

### Growth of dust mites on carpet squares not steam cleaned



### Steam cleaning in the home

The field trial was carried out on a ground floor tenement in Glasgow which was 100 years old, but with central heating. Carpet areas in bedrooms, living room, kitchen and hall were delineated with masking tape. The carpets were about 15 years old. Dust samples were taken from each area, and then one area steam cleaned while another was left untreated. When carpets had dried, another dust sample was taken from each area.

There was no difference in the concentration of Der p1 in dust samples of untreated carpets, but in those which had been steam cleaned there was an average 87% fall in the concentration of Der p1, from 3.3 µg/gram of dust to 0.44 µg/g. But some areas had low concentrations of allergen to begin with, and there were some quite dramatic falls in the areas with the highest concentration.

So if you've got carpets, and problems with allergy in a family member, then it is worth remembering that steam cleaning removes the allergen as well as killing the mites. Technical details about steam cleaning are to be found in the paper.

References:

- 1 S Kalra, P Crank, J Hepworth, CA Pickering, AA Woodcock. Absence of seasonal variation in concentrations of the house dust mite allergen Der p1 in South Manchester homes. *Thorax* 1992 47: 928-31.
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# HIV-1 VIRUS:

## FINDING IT AND STOPPING IT

*Bandolier* is amazed at the rapid changes taking place in HIV monitoring and treatment in recent months. Developments - a test and a treatment - have come together to revolutionise things, with much agonising for purchasers and providers as the speed of the science overwhelms ponderous bureaucracy. This brief review covers only the main points; a fuller version may appear on *Bandolier's* Internet pages.

### Background to HIV infection

When HIV viruses enter cells (lymphocyte or macrophage), viral RNA undergoes reverse transcription to produce double-stranded viral DNA which is integrated into the host DNA. Transcription and translation by cellular enzymes produces large, non-functional, polypeptide chains called polyproteins which are assembled and packaged at the cell surface to produce immature virions to be released.

These immature virions have their polyproteins cleaved into smaller, functional, proteins by HIV proteases, allowing the virions to mature into new active viruses. In 1988 the HIV-1 protease was crystallised and its three-dimensional structure determined. Computer models found chemicals to fit the cleavage site and inhibit protease activity. These inhibitors have been tested in man, and have exciting efficacy in reducing the number of HIV viruses in the body.

### Clinical course

The average time between infection and development of AIDS is about 11 years, but about 20% progress rapidly to AIDS within five years. Another 12% of infected individuals remain free of AIDS for up to 20 years. Viral replication in lymphocytes, some 100 million or so virus particles a day, is associated with the defeat of the immune system. It kills the cells, which is why high levels of virus in blood is associated with low CD4 T-cell levels. Falling CD4 counts herald advanced immunosuppression and AIDS. This defeat of the immune system is associated with the development of conditions like cytomegalovirus infection of the retina, *Pneumocystis carinii* infection of the lungs, or tumours like Kaposi's sarcoma or non-Hodgkin's lymphoma.

Knowing levels of both viral load and CD4 cells is useful in the management of HIV

infected patients. The interaction between CD4 count and viral load in the blood has been likened to an impending train crash, where the viral load indicates the speed of the train and the CD4 cell count the distance to the crash site.

### HIV viral load

Various forms of viral nucleic acid can act as markers for disease progression or response to antiretroviral therapy. Tests have detection limits as low as 500 molecules of viral RNA per mL, but can measure levels above 1,000,000 molecules/mL, covering the range of concentrations of viral RNA seen in patients with HIV and AIDS.

Viral load quartiles (molecules/mL)	Progression to AIDS (%) by 5 years	Median time to development of AIDS (years)	Proportion who died within 5 years (%)	Median survival time (years)
<4,500	8	>10	5	>10
4,500 - 13,000	26	7.7	10	9.5
13,000 - 36,300	49	5.3	25	7.4
>36,300	62	3.5	49	5.1

### Viral load, CD4, and prognosis

Two studies have demonstrated that viral load is an excellent predictor of progression to AIDS [1,2].

The first [1] studied all 209 HIV-1 seropositive men enrolled in a Pittsburgh clinic in 1984 and 1985. Clinical status, CD4 T-cell count and blood samples for laboratory studies were obtained at baseline and every six months for up to 11 years. Results demonstrated a clear relationship between viral load at entry and progression to AIDS and death. Those in the lowest quartile of viral load had only a small chance of progressing to AIDS, and the median time to progression or death

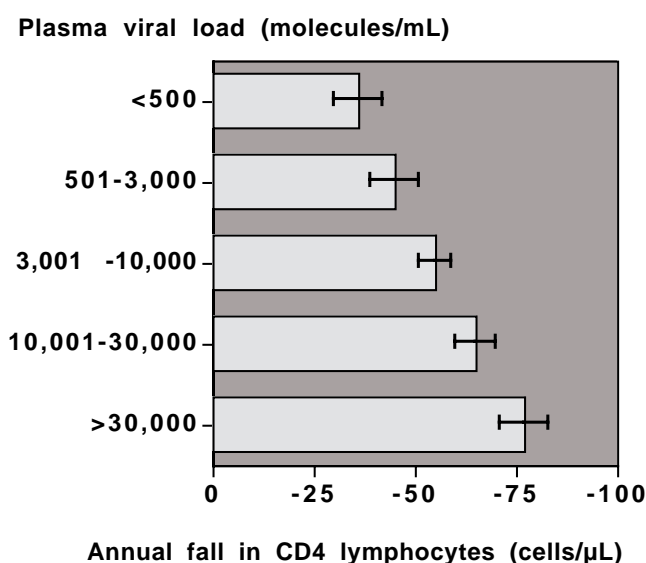
CD4 count (cells/ $\mu$ L)	Viral load category	N	AIDS-free survival (%)		
			3 years	6 years	9 years
>500	I	110	94	82	70
	II	180	96	81	56
	III	237	92	70	42
	IV	202	84	50	25
	V	141	66	28	14
351-500	II	47	96	74	40
	III	105	90	57	31
	IV	121	83	40	16
	V	121	50	20	5
201-350	II	27	93	74	59
	III	44	91	52	27
	IV	53	62	26	11
	V	104	34	9	6
<200	IV	20	50	25	10
	V	70	14	1	0
Viral load category I <500 molecules/mL; II 501-3,000; III 3,001-10,000; IV 10,001-30,000; and V >30,000 molecules/mL					

(>10 years) was limited by the duration of the study. Those in the highest quartile had a high chance of developing AIDS (62% within 5 years) and half died within 5 years.

A larger study in 1604 men infected with HIV-1 concurred [2]. A wide range of markers were compared for their ability to predict progression to AIDS and death over ten years. Five risk categories were defined by plasma viral load - from under 500 molecules/mL to more than 30,000 molecules/mL.

Those in the highest viral load categories progressed most rapidly. But this larger study also demonstrated the effect of plasma viral load on the reduction in CD4 lymphocyte count over time. The higher the HIV-1 RNA concentration, the greater the rate of decline in the CD4 lymphocyte count.

**Plasma viral load is predictive of onset of immunosuppression**



## Viral load and disease progression in infants

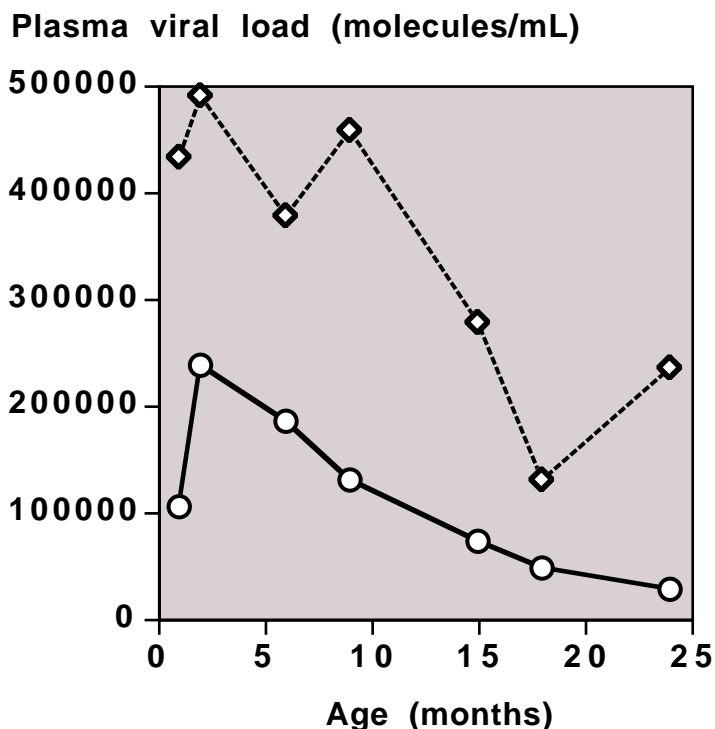
Viral load is prognostic of disease progression in infants [3]. In 106 infants infected with HIV-1 at birth, plasma samples were obtained up to 24 months. Plasma viral load increased rapidly after birth before falling. Infants with a rapid progression of disease had a higher peak viral load in the first two months of life than those without rapid progression.

## Viral load and mother-to-baby transmission

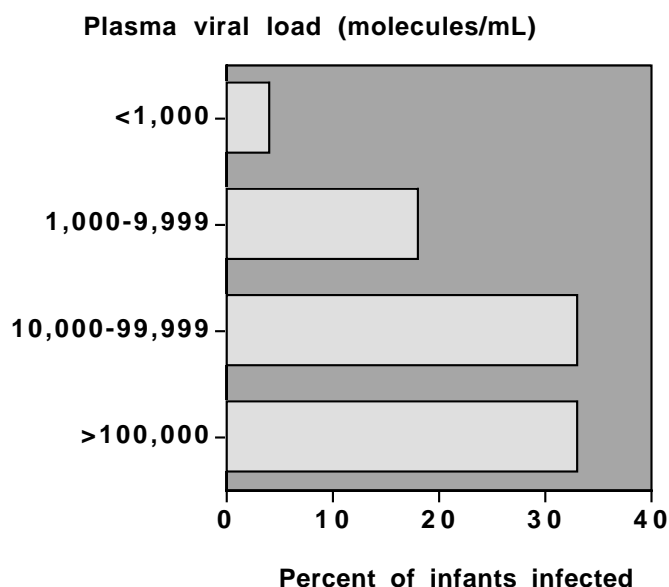
Evidence on mother-to-infant transmission depending on maternal viral load continues to accumulate [4]. Higher maternal viral load gave more infected babies. The study had information on other factors that may affect transmission, like use of abused drugs, unprotected vaginal intercourse during pregnancy, and duration of ruptured membranes, all of which were positively associated with transmission of infection to the infant. Caesarean section may protect from mother-to-infant transmission.

**Plasma viral loads in 106 infants infected at birth where disease:**

—○— progressed rapidly  
 ---◇--- did not progress rapidly



**Mother-to-infant transmission of HIV-1**



## Viral load predicts therapeutic response

Two papers have shown the usefulness of viral load measurement and CD4 counts in predicting success and failure with antiretroviral therapy [5,6]. In randomised trials a reduction in plasma viral load about eight weeks after starting treatment reduced the risk of disease progression by about half. But return to baseline viral load within six months was associated with progression to AIDS [6].

## Viral load models

Mathematical modelling of viral load and disease progression is possible [7]. In the absence of antiretroviral treatment, patients with a viral load of 100,000 molecules/mL are at risk of progression to AIDS in fewer than three years. Those with a viral load of about 300,000 molecules/mL are at risk in less than one year. But with lower viral load, the time to progressing to AIDS extends, so that at 10,000 molecules/mL patients have at least 2.8 years and up to 19 years.

## HIV-1 protease inhibitors

A systematic review of HIV-1 protease inhibitors up to September 1996 has been published [8], as well as a review which puts protease inhibitors into perspective in HIV [9]. There are some important practical points about the use of protease inhibitors, of which there are four - saquinavir, ritonavir, indinavir and nelfinavir (available on a named-patient basis in the UK):

- They may have limited oral bioavailability; saquinavir is only about 4% available, but others, like indinavir, are up to 60% available orally. Patient acceptability of ritonavir may be poor because of the need to keep it cool.
- Drugs that induce cytochrome P450 activity may reduce the availability of some protease inhibitors by increasing first pass metabolism. Drugs that inhibit P450 may increase oral availability.
- There will be complex drug interactions in HIV or AIDS patients on a variety of different drugs, including antiretrovirals.
- Protease inhibitors are associated with a number of adverse effects, including gastrointestinal disturbances and rashes.
- Other adverse effects are more esoteric. For instance, indinavir precipitates in the renal collection system leading to obstruction and symptoms of renal colic, so high fluid intake is recommended.

## Efficacy of protease inhibitors

Studies have yet to appear as full peer-reviewed papers to allow data abstraction. The ACTG 320 trial with indinavir has attracted much media attention because it was stopped early because of good results. Preliminary outcome results are available from the Internet [10].

### ACTG 320 trial

This enrolled 1,156 HIV infected people with fewer than 200 CD4/ $\mu$ L, with over three months experience of AZT and less than seven days experience of 3TC (another antiretroviral drug), and no protease inhibitor experience. Patients were randomly assigned to dual therapy with nucleosides or triple therapy with additional indinavir for about 38 weeks. Baseline stratification was CD4 count of above or below 50/ $\mu$ L.

The rate of progression to AIDS or death was reduced by half in a mean of just 38 weeks of treatment. The number-needed-to-treat (NNT) was 11 for first clinical event for all patients, and as low as 6 for those with very low CD4 T-cell counts of fewer than 50/ $\mu$ L.

### Treatment Guidelines

A consensus statement by the British HIV Association has outlined some broad principles for HIV-treating physicians [11], along with a Drug and Therapeutics Bulletin [12], and recommendations about treatment from the US panel of the International AIDS Society [13]. These were based on the current available evidence, and are suggesting earlier and more aggressive treatment of HIV infection.

Main outcomes of ACTG 320 trial				
Outcome	Percent with event on		Hazard ratio	NNT
	Dual therapy	Triple therapy		
<b>All patients</b>				
First clinical event (AIDS or death)	18	9	0.50 (0.33-0.76)	11
Death	5	2	0.43 (0.19-0.99)	33
<b>CD4 T-cell &lt;50<math>\mu</math>/L</b>				
First clinical event (AIDS or death)	34	16	0.49 (0.30-0.82)	6
Death	9	3	0.37 (0.13-1.04)	17
<b>CD4 T-cell &gt;50<math>\mu</math>/L</b>				
First clinical event (AIDS or death)	9	4	0.51 (0.24-1.10)	20
Death	2	1	0.59 (0.14-2.5)	100
NNT was calculated by: 100/(Event rate dual therapy-Event rate triple therapy)				

## More good news

Three new reports [14-16] bring more good news. The issue is one of reservoirs of HIV virus, where latent infection of CD4 cells may occur despite apparently low viral loads in blood, or lack of symptoms.

As few as 5 and 7 cells per million may be infected in lymph nodes and blood respectively. The mean frequency of macrophages containing integrated HIV-1 DNA was 54 cells per million. So what happens when triple therapy apparently clears the virus from the blood? In eight patients starting treatment, HIV-1 in plasma dropped by more than 99% in the first two weeks due to rapid elimination of the free virus and loss of productively infected cells. About 2.3 to 3.1 years of treatment with a completely inhibitory regimen would be needed to completely eliminate HIV-1 from these longer-lived compartments.

Serial tonsil biopsies from ten patients treated with triple therapy showed that the amount of HIV-1 virus dropped rapidly. After 24 weeks more than 99.9% of virus had been cleared from the lymphoid tissue reservoir.

## Comment

All of this is exciting stuff. If the fight against HIV and AIDS has seemed in the past to be like trench warfare, with every yard being hard fought, the new combination of effective tests for viral load and the advent of protease inhibitors seems like a cavalry charge. Ground is being gained, but the battle, let alone the war, is far from over.

Many challenges remain. Perhaps the most important is drug resistance in viruses, and the need to ensure compliance with therapy. But adverse effects, and the complex pharmacokinetic and pharmacodynamic interactions of these complicated therapies will challenge the clinical skills of those treating individuals with HIV and AIDS.

The other is cost. In the UK a patient going from no treatment to triple therapy would increase costs of drugs and tests by about £10,000 a year. Will the savings offset the costs? We have to wait for more information. But there are signposts that can help us look ahead. For instance, the balance of costs to society of a young man or woman in employment paying taxes becoming ill and unemployed, not paying taxes, and consuming healthcare will likely favour keeping them healthy. Treating some AIDS-related disorders, like cytomegalus infection of the retina, is hugely expensive.

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## KING'S FUND

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### Mental Health in the City

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An international conference hosted by the King's Fund and the Bethlem and Maudsley NHS Trust, 27-29 October 1997, London. Through a combination of plenary sessions and workshops, this major 3-day event provides an international perspective on the progress being made in developing mental health services in inner cities around the world.

How do 10 major cities around the world tackle rising mental health problems?

What can users contribute to mental health services?

What can be learnt from their experiences?

For a brochure and application form, please contact Silvia Roberts at the King's Fund on 0171 307 2592

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