



Paediatric HIV Care





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Forward

Research in HIV-1 paediatric infection is limited in breadth and scope compared to that pertaining to adults. Research on the antiretroviral treatment of children has, although often years later, identified the same factors in children as critical for successful treatment as have been identified in adults.

These factors, viral resistance, potency of the drug regimen, therapeutic drug monitoring, and adherence to the regimen, are mentioned in the i-Base introduction. As they also mention, incorporating 'recent findings' and 'new insights' into the care of children with HIV has often lagged behind that of adults. And although, not explicitly stated, they imply, that all involved should aspire to excellent state-of-the-art care for HIV infected children.

HIV i-Base contributes to this effort by organising educational meetings and by publishing summaries and discussions of important research.

Paediatric HIV providers have the difficult task of evaluating research conducted in adults and deciding which aspects warrant translation, prior to the repetition of similar studies in children.

Rapid implementation of certain findings to paediatric care seems warranted when there is a significant potential benefit to children, or when harm might result by ignoring the findings. Because children are different from adults, careful consideration of studies done in adults is necessary to determine their 'paediatric relevance'.

Conscientious experts need to lead the paediatric community in this endeavor so that we provide the best care possible to all infected children.

Lisa Frenkel and Stefano Vella

Co-chairs

Introduction



As we go to print, the most comprehensive published guidelines for treating children with HIV, *The US Guidelines for the Use of Antiretroviral Agents in Paediatric HIV Infection*, are already over a year old, and unreflective of the clinical care provided by many of the contributors to this report. Whilst guidelines in any fast-changing medical field such as HIV will always lag behind the latest research, it is unfortunate that a similar monthly review and support network to that for adult care is not available.

In the UK advocacy for adult care (for example - access to triple therapy, to viral load and resistance tests, TDM, the importance of aiming for undetectable viral suppression below 50 copies/ml, early switching of failing regimens etc) was something of an uphill struggle. One of the current concerns in adult care is that treatment success, whether for first-line or subsequent therapies, is dependent on several key factors, none of which can be ignored. Potency, resistance, drug levels and adherence are all essential parts of the equation, and that this is similarly being realised in paediatrics, and is reflected in the presentations from this meeting, is very encouraging.

Children have been frequently treated with combinations that are insufficiently potent to suppress the virus, quickly leading to the development of resistance. At one time it was thought unrealistic to aim for maximal suppression due to childrens' higher viral load but, again optimistically, this view has also changed. We highlight strategies that start treatment with potent 4-drug regimens from both UK and US clinicians that are aiming for and achieving higher success rates. And although resistance tests for adults have now been integrated into standard of care, and despite identical reasons for accessing them, this is not the case yet for children.

As we all hope, and Di Gibb explained, 'these children are going to live for at least twenty or thirty years' but 'they have run out of everything in two and we know from data that you are half as likely to respond to your second regimen as your first.'

Long-term use of antiretroviral therapy is raising new concerns of associated toxicity. The meeting included an important presentation on lipodystrophy - and that likelihood that it is currently being under-diagnosed - together with a discussion on Strategic Treatment Interruptions as a strategy to manage long-term treatment.

In the UK we have one of the world's foremost pharmacology departments at Liverpool University, but the support services it offers to all UK clinics for therapeutic monitoring of antiretroviral drugs are still under-accessed. For paediatric care, where optimal dosing is notoriously difficult to determine, TDM for any PI or NNRTI should also be standard of care, as is the case in both France and Holland. Most importantly, subsidised programmes provided by Roche and Merck will ensure that all costs for this service are covered for all children using nelfinavir, saquinavir or indinavir including combinations. The appropriate form and contact details are included in Appendix VI for clinicians that have yet to access this service.

The central role of adherence in the success of any treatment is stressed over and over again. We look at the importance of support within the community and at practical ways to make medicines easier to take, like using g-tubes and teaching pill swallowing.

But even at 44-pages, this report left out a lot of material from the discussions and presentations. We believe there is an important role for, and would love to see, a regular international meeting on the subject of paediatrics - would anyone like to take up the challenge?

Finally we were, as always, completely blown away by the generosity of our speakers. Some who were prepared to fly half way round the world (or in the case of UK paediatricians, risk the wrath of their own families during a half-term holiday), to speak at a meeting, organised by activists, that in a few cases they had never even met.

You have our warmest thanks.

Polly Clayden and Simon Collins, HIV i-Base

Optimising treatment for HIV-positive children

Lisa Frenkel MD



Children have frequently been treated with antiretroviral combinations that are insufficiently potent to suppress the virus, leading to resistance. This leading US paediatrician treats with more complex therapy upfront as well as in a salvage setting.

While many children have experienced recoveries that are genuinely 'miraculous' in association with HAART, we know that, unfortunately, the results have not been universally successful. In particular, treatment has 'failed' those children who developed resistance to combinations that were insufficiently potent to maximally suppress the virus. Treatments demand a high level of adherence (>95%) to avoid the selection of drug resistant virus and for other children, adverse reactions from the drugs have been intolerable.

Our aim is therefore to determine regimens that suppress viral replication, minimise side effects and that are practical for a child's lifestyle. Achieving these therapeutic goals with the currently available antiretrovirals has to overcome difficulties of adherence, the presence of drug-resistant virus from previous therapies, cross-resistance to drugs within each class, and the toxicity profile of individual treatments.

Paediatric care is based on limited data. Neither an optimum combination nor time to initiate paediatric HAART has been defined. The treatment of primary infection in infants appears beneficial [1], but this has not been compared to delayed HAART. Furthermore, the frequency and severity of adverse reactions associated with various treatment strategies (early vs. delayed, and continuous vs. intermittent), has not been evaluated either in the short or long term.

Early 3-drug studies

Nevertheless we have some data to work with. Early comparative trials of HAART with two nucleoside analogues and a protease inhibitor demonstrated superior clinical benefits in adults to dual nucleoside therapy [2]. Subsequently, studies were designed to evaluate the suppression of viral replication, instead of clinical outcomes. This occurred for multiple reasons, including the association of low viral loads with slower HIV-1 disease progression in multiple studies [3-5], the ease in evaluating plasma HIV-1 RNA levels, and the recognition that if viral replication was not suppressed to very low levels selection of drug resistant virus would occur within weeks to months.

Although the superior virological benefit of three drug over dual regimens was clearly shown, early studies of three-drug HAART in nucleoside experienced children resulted in suppression to HIV-1 RNA <400 copies/ml in only 25-42% of children [6-9].

4-drug regimens

There have been few comparative trials between different HAART combinations in children. However, in reviewing both

the comparative and observational studies, four-drug HAART regimens, including treatment experienced children, have demonstrated higher rates of viral suppression compared to three drug regimens.

Four-drug regimens in the ACTG 377 and ACTG 382 studies, which also included children with previous nucleoside experience, provided greater virological success (61% <400 at week 24 in ACTG 377 and 76% <400 at week 48 in ACTG 382). However both three and four-drug regimens in these studies included all three classes of agents, leaving limited salvage options for the children whose treatment failed to achieve an undetectable viral load [10, 11].

Trials comparing three- and four-drug HAART in sequential cohorts of antiretroviral naive infants are ongoing, and preliminary reports also suggest that four-drug therapy offers greater antiviral benefit over three-drug regimens.

Arguments against the use of four drugs in an initial HAART regimen are based on several reasonable suppositions, namely, that adherence to therapy could decrease as the number of drugs increase, that adverse reactions and toxicity could be increased, and that the initial use of four-drug HAART leaves the child with less of a chance for successful 'salvage' therapy. While the data examining these issues is meagre, it does not support these suppositions, and they have not been reflected in adult care.

Toxicity was *not* increased among children taking four-drug compared to those taking three-drug HAART in ACTG 377 study and discontinuations were higher in the 3-drug arms, primarily due to insufficient viral suppression. Adherence to the regimens was not evaluated in this study, however, the superior antiviral effect of the four-drug HAART suggests that adherence to the former was not significantly compromised.

Salvage therapy

Salvage therapy has been less well studied but adult care has produced several important general lessons, including the importance of early switching and using greater numbers of accurately targeted agents. Nevertheless, the efficacy of salvage therapy has generally been inferior to the initial therapy of untreated individuals in all studies.

Preliminary analysis of one study of salvage therapy for children indicated that it was not effective in children previously treated with three-drug HAART that included protease inhibitors (ACTG 366) [12]. Only 10% of 100 PI-experienced children had their plasma HIV-1 RNA replication suppressed to <400 copies/ml 12 weeks after a four-drug regimen including

nucleoside analogues not previously used, nevirapine and a protease inhibitor.

Limiting the time ongoing therapy is continued after viral rebound by earlier detection and frequent monitoring of plasma HIV-1 RNA has the potential to improve the outcome of a subsequent salvage regimen. In addition, mega-HAART treatment with five or more antiretrovirals, can suppress viral replication in antiretroviral-experienced children, if they do not have high-level resistance to protease inhibitors, and assuming that they are highly (>95%) adherent to the new regimen.

Salvage therapies have not yet been systematically studied in children but in this area we should closely follow and learn from the results of adult care. While there are immunological differences with children, the virological mechanism of resistance is likely to be very similar.

Dosing and PK

Correct dosing for each drug used in antiretroviral therapy also needs to be defined. The ACTG 382 study demonstrated that levels of efavirenz and nelfinavir were lower than expected in young children [11], pointing to a common theme with antiretrovirals in young children. Other studies have found lower levels than expected of ritonavir, nelfinavir, and nevirapine in young infants. Didanosine levels have been very variable in children [13]. These data argue, not only for age-specific doses, but therapeutic monitoring of drug levels might be necessary for optimal management of HAART in children.

The focus on virological suppression in most studies has sometimes lead to the immunologic benefits with only partial suppression of replication being overlooked. The determinants of immunologic recovery have not been defined in children but are likely to be age dependent. Adults with incomplete but sustained suppression of viral replication by HAART to RNA levels below their viral set point have immunologic benefits [14]. Importantly, the duration of these benefits have not been characterized.

In young children, I have observed a prolonged (>3 years) immunologic benefit in spite of high level viral resistance and return to baseline plasma HIV-1 RNA levels. These observations suggest two phenomena that require definition. First, the spectrum of immunologic benefits provided by lowering the level of viral replication, and second, the parameters affecting immune reconstitution in children and its natural history once achieved.

When to start - and with what

The available data has led me to advocate the initial treatment of infants and children with four-drug HAART, including two NRTIs, one NNRTI and one PI. Care in dosing the protease inhibitor should be taken to ensure that levels will be sufficiently high throughout the day and night, and lopinavir/r has many advantages in this respect. This is usually combined in a twice daily regimen with lamivudine, stavudine and nevirapine, as these agents are generally well tolerated. A very high level of adherence is necessary to obtain the maximum benefit from any HAART regimen [15].

I do not recommend therapy until there is at least a moderate degree of immunodeficiency or HIV-1 related symptoms, and until the family is in full agreement with therapy and is confident

in their ability to administer antiretroviral treatment. Due to the difficulties in administering multiple drugs, some with unpleasant tastes, I introduce and encourage the use of gastrostomy tubes, unless the child can easily (and willingly) swallow pills.

Frequent monitoring of plasma HIV-1 RNA, (at least every month) especially early after treatment is initiated provides the opportunity to modify, intensify or stop therapy if plasma RNA levels do not progressively decrease. Using this strategy the child's HIV-1 generally does not develop multi-drug resistance, and the antiretroviral regimen can usually be manipulated so that viral replication is sufficiently suppressed by this allowing adequate immune reconstitution to occur and achieve good health.

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Treating HIV-positive children: the Dutch perspective



Professor Ronald de Groot

Paediatric care in the Netherlands is highly individualised and supported. They report high success rates with early therapy, view development of resistance as disease progression and integrate drug level monitoring into all paediatric regimens.

In 1997, the increasing number of children with HIV/AIDS stimulated the three centers in the Netherlands (in Utrecht, Amsterdam and Rotterdam) to start a collaborative open-labeled multicenter trial. This was to evaluate the clinical effects, the virological response, pharmacology of antiretroviral agents and the extent of immunoreconstitution, in response to triple therapy with indinavir, zidovudine and lamivudine.

We formed a multidisciplinary team of experts in immunology, virology, HIV pharmacology, internists specialised in HIV/AIDS and paediatricians in order to be able to rapidly implement new insights in the field of care and research. In addition we assembled a multidisciplinary team caring for the children and included nurse specialists, a social worker, a psychologist, research physicians and paediatricians.

We also intensified our contacts with organisations in the community, which are involved in the health care or social care for children with HIV/AIDS. The leading principle in the design of the triple therapy study was that care should be organised in a structured way and that the research questions should only be raised, when they serve to improve the quality of life of children with HIV/AIDS.

Dutch multicenter triple therapy study

Currently more than 40 children in the Netherlands have been included in the study using a combination of indinavir, zidovudine and lamivudine. Approximately 50% of these children were pretreated with a NRTI, whereas the other 50% were naive. Eight children continued to be followed within the trial after they switched from indinavir to nelfinavir.

The clinical results of the treatment have been very good. Since the introduction of triple therapy in 1997 only one child has died, who was already at a very advanced stage of disease at the initiation of therapy. All other children are in a good clinical health.

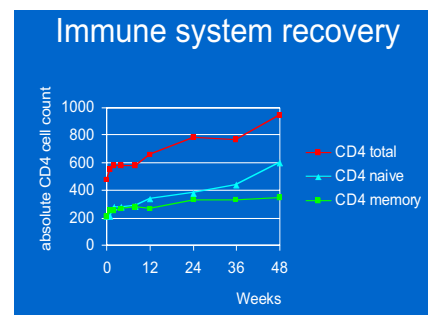
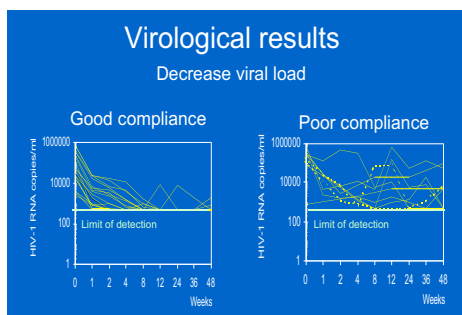
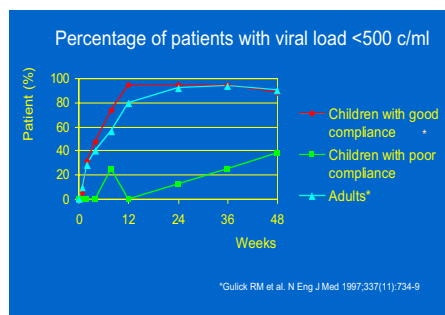
The 2-year follow-up data indicates, that 69% of the children have a viral load below 500 copies/ml, and that 50% have a viral load below 40 copies/ml. These results are comparable with those obtained in adults on HAART in our country. It should also be remembered that these results were obtained from an unselected population: all children with HIV/AIDS, who fulfilled the criteria for entry, were enrolled.

We extensively studied the pharmacokinetics and pharmacodynamics of the protease inhibitors used in this study (indinavir, nelfinavir, ritonavir). The data showed a large variability in pharmacokinetics between different children at different ages. This underlines the importance of pharmacological analysis in *all* children on HAART. We adapted our dosing regimens when the AUC was significantly higher or lower than the optimal AUC used for adults.

We strongly believe that regular drug monitoring forms a routine part of the optimal care for children with HIV/AIDS. The good clinical results that we achieved are also reflected by the findings from a study showing immunoreconstitution in virtually all children (see page 23 of this report).

We observed a full recovery in the number and percentage of CD4 naive and memory cells. Interestingly, we also found this discovery in a small subset of children with virological failure (viral load > 500 copies/ml). In contrast to studies in which dual therapy with NRTIs was given, we also see a catch-up growth in length and weight to normal values for age.

The two-year follow-up data show that a significant percentage (38%) of the children had problems in maintaining adherence. The link between virological response and adherence in children was shown very early in a study by Gulick and colleagues in 1997 and we found similar results - see Figure 1 and 2. We therefore sought to optimise therapy adherence by means of structured discussions with parents and children,





using booklets in which stickers were applied after dosing, drug monitoring, etc. In addition we have recently written new protocols that change 3 or 4 times daily regimens to a twice-daily regimens. We have also introduced electronic pillboxes in order to offer additional information on therapy adherence.

Future studies

We are convinced that twice-daily regimens and (in the future) once-daily regimens of HAART may contribute towards a better therapy adherence. We are currently initiating new studies in which twice-daily therapy with a NNRTI and dual PIs are used. Because of the central role of adherence in the success of treatment we have also set up studies to analyse the social background of our patients and their individual ability to cope with HIV.

These studies may lead to the delineation of patients with a risk profile, where more intensive support should be offered. In addition we will seek to study more basic questions such as why immunoreconstitution in children on HAART seems to be better, than in adults and why prepubertal children are relatively protected from lipodystrophy.

The international perspective

We have initiated a collaborative study with the Department of Paediatrics in the Children's Hospital in Düsseldorf (Germany) with Dr. Horst Schroten and Dr. Tim Niehues. We also are involved in two projects in Romania in which we will offer treatment to children with HIV/AIDS.

One of the difficulties in paediatric HIV research is that the number of patients in western European countries and in the USA are decreasing as a result of the success of antiretroviral treatments available to pregnant woman. This means, that a large number of institutions (and investigators) will be necessary in the future to answer questions regarding the efficacy of new antiretroviral regimens.

In this respect one may question whether it is really necessary to perform controlled studies. Novel possibilities for therapy may perhaps be postponed due to the relatively small number of children able to enrol in a study. The PENTA group certainly has a major role to play and needs to consider these facts and to design studies which primarily contribute towards better care and quality of life for children with HIV/AIDS.

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Paediatric use of ABT-378/r (lopinavir/r)



Octavio Ramilo

In view of the number of children that have already developed resistance to current PIs, the difficulties associated with currently available formulations, and the recent availability of an expanded access programme in Europe, we wanted to include a presentation in the meeting from an independent investigator with experience of lopinavir/r in a paediatric setting.

Paediatric M98-940 study

The objectives of this Phase I/II dose-ranging international paediatric study were to evaluate the safety, tolerability and the antiviral activity of lopinavir/ritonavir in combination. This combination is also referred to as ABT-378/r or the trade name Kaletra and is available as liquid formulation for HIV infected children.

The ratio of lopinavir to ritonavir (4:1) is the same in both the paediatric and adult formulations. The pharmacokinetic enhancement from ritonavir increases the peak levels, trough levels and total exposure (area under the curve, AUC), and a prolonged dosing half-life allows a cushion period for some flexibility from a strict Q12H dosing regimen. The ritonavir dose in this formulation is not being used for an antiretroviral effect.

For the entry criteria in the paediatric study we convinced Abbott to be quite open and the children were between three months and twelve years of age. They had to have detectable plasma HIV RNA, and be NNRTI-naïve but there were no limitations in terms of CD4 count or other previous treatments.

Children were considered treatment-naïve if they had less than three months of therapy or less than one week of 3TC - otherwise they were considered experienced. The regimens chosen were based on the previous experience with adults.

Treatment-naïve children received lopinavir/r plus d4T and 3TC. Experienced children received lopinavir/r plus nevirapine and either one or two NRTIs chosen by the individual investigators. The two doses were chosen to achieve the same drug exposure as in adults with a standard 400mg/100mg dose. Children were randomised to either 230/57.5mg/m² lopinavir/r every 12 hours or 300/75 mg/m² lopinavir/r. They were also stratified to age (<2 yo and >2 yo) and therapy (experienced or naïve).

Fig.1 - Baseline demographics

	Naïve (n=44)	Experienced (n=56)
Age		
mean (years)	4.8	5.7
range	6 mo - 10.2 yrs	8 mo - 12.6 yrs
< 2 years (n)	8	6
Gender		
male	18 (41%)	25 (45%)
female	26 (59%)	31 (55%)
Perinatal infection	43 (98%)	53 (95%)

After half of the children in these groups received at least three weeks of therapy there was an interim analysis for safety, tolerability and efficacy. At that time it was found that both groups had the same tolerability and the same antiviral efficacy. Because of previous results in adults, and a concern for lack of adequate potency, the decision was made to choose the higher dose. The baseline characteristics are shown in Figures 1 and 2.

In contrast to most adult studies which usually have at least 70% males, we had a slightly higher number of girls. There was a wide range of viral load between 2.6 and 7 log (10 million copies/ml). The mean viral load was statistically significantly higher in the naïve group (4.9 vs 4.5 logs) and this was also reflected in the difference between CD4 percentage (21.6% vs 26.3% respectively).

The majority of the 56 experienced children had been exposed to AZT/3TC. Children with PI experience had been exposed to most regimens, including abacavir. Almost a third of the PI-experienced patients had used more than one PI.

Approximately half the children were included in the PK analysis including 13 patients under two years of age. Interestingly there was no association between age and drug levels or clearance.

We learned quite rapidly, and this was confirmed with efavirenz in adults, that NNRTIs induce the metabolism of lopinavir/r. So children that got nevirapine in combination with the low or the high dose of lopinavir/r had decreased PK parameters, with trough concentrations that were down by 30% to 40%.

If you use the low dose without nevirapine you get approximately the same drug levels as adults and if you need to use nevirapine then you probably have to jump up to the higher dose. Based on these findings the FDA approved this agent and they recommended an initial dosing in mg/kg which is approximately equivalent to the lower dose evaluated in the

Fig.2 - Baseline characteristics

	Naïve (n=44)	Experienced (n=56)
HIV RNA (log₁₀ copies/mL)		
Mean* (Range)	4.9* (2.6-7.0)	4.5 (2.7-5.8)
CD4 cell count (cells/mm³)		
Mean (Range)	920 (40-3,340)	773 (15-2,595)
CD4 %		
Mean* (Range)	21.6* (2-38)	26.3 (1-46)
Immunologic Categories		
I. No suppression	50%	73%
II. Moderate suppression	39%	14%
III. Severe Suppression	11%	13%

*p<0.05

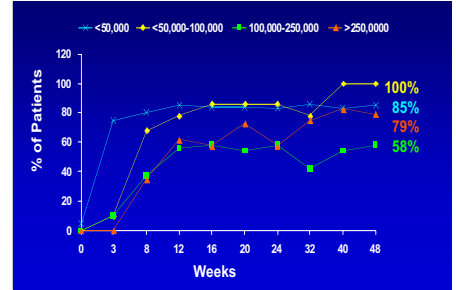
Figure 3. M98-940 - adverse events

Adverse events of at least moderate severity and probable, possible or unknown relationship to Lopinavir/r	
Body as a whole	n
Allergic reaction	1
Fever	1
Viral infection	1
Digestive System	
Constipation	1
Pancreatitis	1
Hepatomegaly	1
Vomiting	1
Skin	
Dry skin	1
Rash	2
Special Senses	
Taste perversion	1

Figure 4. M98-940 - Grade 3-4 lab abnormalities

Laboratory parameter	n
Sodium (< 130 mEq/L)	3
Neutrophil count (< 0.40 x 10 ⁹ /L)	2
Platelet count (< 50 x 10 ⁹ /L)	4
Total bilirubin (> 2.9 x ULN)	3
ALT/AST (> 10 x ULN)	3
Total cholesterol (> 300 mg/dL)	3
Amylase (> 2.5 x ULN)	6
Pancreatic amylase (>2x ULN)	1

Figure 5. % <400 stratified by baseline viral load



study 230/57.5mg/m² lopinavir/r BID, however this is currently being revised. Personally, in view of the good tolerability and in an attempt to optimise its antiviral activity in treatment-experienced children I would prefer to use the higher dose (300/75 mg/m² BID) evaluated in the study.

Safety and side-effects

Of a hundred children enrolled in the trial there were only two discontinuations. One occurred in the first 24 weeks, a five year old child in Panama, who developed lymphoma in the first month of therapy and for that reason the drugs had to be stopped. Although he received chemotherapy he did not survive more than two weeks. The other discontinuation, and this one is related to the study drug, occurred in South Africa and was a child who developed pancreatitis. This child had elevated amylase before enrolling on the trial.

Figure 3 shows a summary of all the adverse events of at least moderate severity of up to week 48 which were remarkably low - single cases of pancreatitis, hepatomegaly, some vomiting, rash and fever.

It was interesting that we had only one child that complained about the flavour as reported in the adverse events section, who was one of my patients, but she did not stop taking it.

Grade 3-4 laboratory abnormalities are shown in Figure 4. Some of them reflect some of the baseline characteristics - like the child with lymphoma had neutropenia. Two children had to stop therapy: one because of an increase in ALT and one because of an increase in amylase. All the children with increases in amylase also had increased baseline amylase and the majority of these children were from Panama and South Africa with advanced disease.

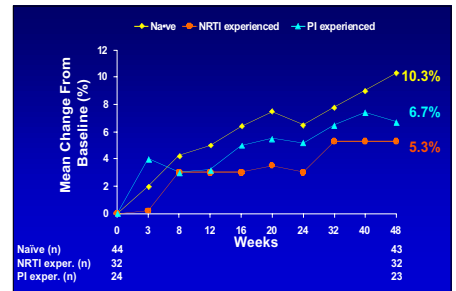
With cholesterol levels, three children went above 300 mg/dL. Two of them had baseline cholesterol of about 300 mg/dL. One went up to 325 mg/dL and then became normal. The impact on the lipid metabolism is one aspect that we definitely need to learn more about - but these results were definitely much better in terms of the laboratory abnormalities than those seen in adults.

Virological results

In the first three to eight weeks there were similar results between the naive and experienced children, but we then saw a trend that becomes very clear by week twelve as PI-experienced children were not responding as well as the others.

By week 48 (ITT analysis), 84% of treatment-naive children had viral load reductions to <400 copies/mL. This was 88% among

Figure 6. M98-940 - CD4 response



those who were nucleoside-experienced and 58% among those who were PI-experienced. Remember though that a third of these kids have used at least two PIs previously. When we look at the data to <50 copies/mL the results were 69%, 71% and 54% in these three groups respectively, and this is still very impressive.

The response <400 copies (ITT analysis) was analysed on the basis of the baseline viral load in four groups:

<50,000	85%	n=52
50-100,000	100%	n=9
100-250,000	58%	n=20
>250,000	79%	n=19

Figure 5 shows that with lower viral loads the response occurs very rapidly. It took longer to get <400 copies/mL for children with a baseline >100,000 copies/mL but still the percentages were very good. Overall there was a trend suggesting a lower viral load at baseline predicted a greater likelihood for achieving viral loads <400 copies/mL.

Conclusion

Based on the current data we concluded that the liquid formulation of lopinavir/r appears to be safe and well tolerated in HIV infected children.

We only had one drug related discontinuation, a few adverse events and three or four laboratory abnormalities. Lopinavir/r appears to demonstrate a substantial viral efficacy in both naive and experienced paediatric subjects. According to the intent-to-treat analysis 84% of the naive and 75% of the experienced achieved less than 400 copies/mL.

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NNRTI-based and PI-sparing 4-drug combinations

Hermione Lyall

Children with advanced HIV at St Mary's are also treated with 4-drug combinations in first line, using an NNRTI and three nucleosides. This offers a potent alternative to using 4-drug combinations with all three classes.

Although the use of NNRTIs in first line therapy (without PIs) has not been well studied, this may be an ideal role in which to use them, especially in a four-drug combination.

A preliminary study of the three-drug combination of AZT/3TC/nevirapine in six children (age 2-4 months, baseline viral load 40,000-1,500,000 copies/ml) produced an early reponse to <10,000 copies/ml by day 14 but this was sustained to 24 weeks in only two children. [1] This also highlighted ongoing concerns in paediatric care of previous treatment or exposure to antiretroviral drugs and relatively high levels of viral load replication.

Nevirapine has been available in the UK since late 1997. The liquid formulation is palatable and can be used in once or twice daily regimens.

We have recently reviewed the use of nevirapine in a mixed group of seventy-four children. Only 28 of these children were treatment naïve and, as reflects the majority of our cases, about 70-80% of the children were of African origin. Both the naïve and pre-treated group were starting from high viral loads and low CD4 counts and low z-scores.

At 24 weeks, 60% of treatment naïve children were <400. Now we would be aiming for lower levels still, but at the time this was not too bad. With pretreated children the success rate was much lower (approximately 38% <400copies/ml). [2]

We then went back through all the case records to see the dosing the children had received. At that time the recommended dosing was 240-300mg/m²/day but many children received lower doses. This analysis revealed a direct relationship between dosing and efficacy with only those children receiving >300mg/m²/day achieving viral load <400 copies/ml for all the children in that group. This is very important. Underdosing in paediatrics is now increasingly recognised as an important problem.

About 20% of children showed any incidence of rash, with grade 3-4 in 5% of the children. Median time to onset was nine

days (range 1-44 days). There was one child who got quite severe transaminitis and five cases of grade 3-4 neutropenia.

In PACTG 383 with efavirenz (plus nelfinavir and at least one RTI), 58% of 18 treatment-experienced children achieved viral loads levels <50 copies/ml at 48 weeks. This may be better but it is still not good enough – and again raises the question of the difficulty of a salvage regimen for those children whose treatment did not produce optimal results, and who developed resistance to all three classes.

This study again showed that antiviral effect was related to dosing levels. Importantly in this study there were particular difficulties with dosing for efavirenz and nelfinavir in the ten children who were under two years of age – seven and five of whom had suboptimal levels of efavirenz and nelfinavir respectively. [3]

Although I agree that with advanced children you have to use at least four drugs in a combination, I have serious concerns about using all three classes of drugs in a first-line therapy. I think it is better to only use two classes of drugs, then having the opportunity of one held in reserve for the next time round.

We have a small cohort at St Marys of five children (median age 3 months, range 1-28 mo) who presented with AIDS defining illnesses (4 cases PCP, 2 cases CMV retinitis, 1 case bacterial pneumonia). With these children we used a four drug combination using two classes of antiretrovirals (nucleoside analogues) abacavir, 3TC, AZT and nevirapine (non-nucleoside analogue).

These children all had very low baseline CD4 counts that have since come into a more or less normal range. All five achieved viral load <100 copies/ml at a median of 19 weeks (editors note: which has since been sustained for a further four months). They were all underweight and thin before starting treatment and have seen dramatic improvements in their weight. There were three case of rash although this led to no discontinuations.

Although there are few studies of NNRTIs as first line therapy for children, there is evidence from adult studies that NNRTIs can be included in an effective first-line regimen even with relatively high viral loads.

The advantages of this regimen include easier dosing and achievement of good therapeutic levels. If you are going to be using PIs in children you also need to use therapeutic drug monitoring. The liquid formulations for nevirapine and efavirenz are palatable and nevirapine tablets are crushable, dividable, soluble and easy to manage.

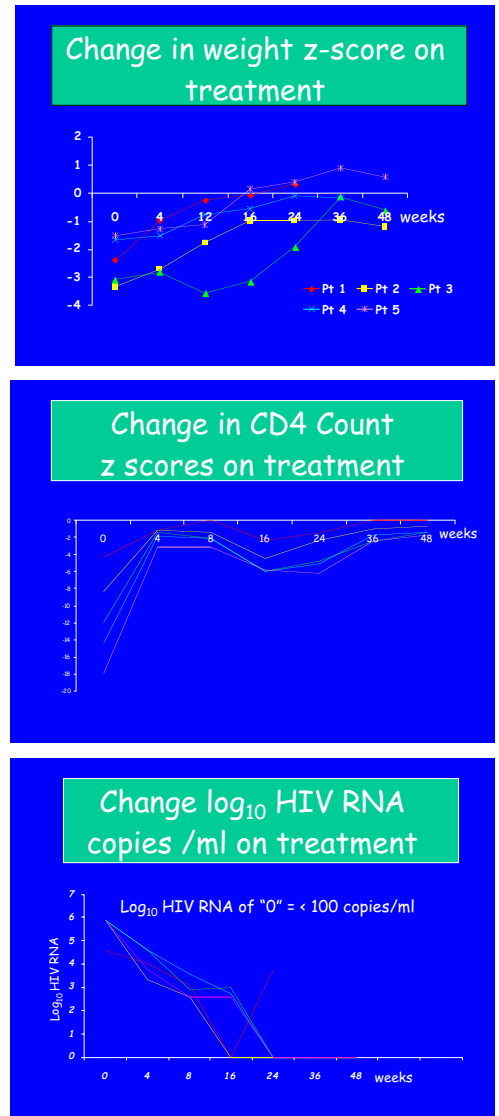
In general, NNRTIs have less GI side effects and that is obviously important for children who are meant to be eating, growing and gaining weight. There is also a concern with the long term metabolic side effects that we are beginning to see in adults who have been on PI treatment for 2-3 years, particularly related to cardiovascular events, glucose metabolism and more recently osteopenia.

If we are starting small children on these drugs then what's going to happen to these kids when they are teenagers and young adults? This is something that should be an ongoing concern.

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Figs 1-3. Changes in parameters in children [4]



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Therapeutic Drug Monitoring (TDM) in the Netherlands



David Burger

With drug concentrations in paediatrics being so variable, and virological response being so closely linked to these levels, there are enormous practical benefits to using TDM. Every HIV-positive child in Holland receives these tests as part of routine care, including a full PK curve when they begin treatment.

TDM is available for routine adult care in the Netherlands and we believe that its use in paediatric care is essential. This presentation will focus on the practical benefits that we have been able to provide through this widespread use of TDM.

While there remain concerns about assay validation as laboratories broaden the availability of this technology, the relationship between plasma levels of protease inhibitors and virological effect is certainly apparent. The following studies also show that achieving optimal drug levels cannot be taken for granted for some of the key protease inhibitors currently used in clinical practice today.

The traditional view of TDM is that pharmacologists and clinicians look at the drug and its characteristics and decide that the drug needs therapeutic drug monitoring. A more modern view of TDM, proposed in a paper two years ago, is that it is the patient rather than the drug that determines TDM, so you need to look at the patient using that drug in a specific indication.

In practice TDM is inappropriate for RTIs due to the difficulty of measuring intracellular phosphorylation, but for the PIs and the NNRTIs the situation is different. These drugs are active in the plasma compartment and can be measured by HPLC or by LCMS. These assays are generally 'Home Brew' methods developed by laboratories in different countries, and so validation and quality control has become an important issue.

Therefore, an international quality control programme was established to standardise and validate the results from these laboratories. This involves an ongoing 6-monthly evaluation of blinded samples and the results from the first assessment are shown in Table 1. It is clearly important that we are sure that these labs are measuring drug levels accurately. Results from a second round of this programme, including nineteen laboratories, will be reported at the Retrovirus Conference in February 2001.

Drug levels and pharmacological response

Three years ago we looked at a group of 65 adults using indinavir in the original 800mg TID regimen. We found three risk factors

that were independently related to virological failure: a very low indinavir drug level in plasma, high baseline viral load when starting treatment and whether previous treatment included a PI. [1]

Table 2 shows the results from subdividing this group by risk factors in order to determine the influence of the drug levels. For people most likely to respond to treatment – those who were PI-naïve with a baseline viral load <100,000 – drug levels made little difference to the risk of non-response (at around 10%). In a similar way, drug levels made little difference for the people who were least likely to respond. All of the patients who were PI-experienced and had a high baseline viral load failed to respond, irrespective of drug levels.

In this study, the importance of adequate drug levels became significant for people in between these extremes. With patients who were PI-naïve but had a high viral load, adequate drug levels made a difference in risk of non-response of 9% compared to 56% with suboptimal levels. Optimal drug concentration in people with PI-experience and low viral load levels lead to a 20% rather than 50% risk of failure. With treatment success depending on other variable factors, accurately identifying patient groups most likely to benefit is therefore important.

Some of the same relationships were shown in a paediatric study conducted in Rotterdam, Utrecht and Amsterdam. This study with indinavir showed a clear relationship between virological response (defined as viral load <500 copies/ml at 6 months) and AUC. There was a 55% response rate in children with AUC <20mg/L/h. The response rate was 100% in children with higher AUC levels >20 mg/L/h. This led us to set a minimum target level of 20 mg/L/h in this population.

Drug levels and side effects

The same study highlighted the relationship between drug levels and risk of side effects. The six children who had renal side effects in this study had a much higher AUC compared to the children without (mean 40.6 mg/L/h vs. 21.6 mg/L/h). Similar results associated risk of renal side effect with both AUC and Cmax were

Table 1. QA and QC assay programme

Results of International QC program		
(1 st Round, 9 labs, 3 samples)		
Inaccuracy (%)		
	median	range
IDV	9.9	2.4 - 32.7
NFV	21.4	9.2 - 29.6
RTV	22.9	3.1 - 60.4
SQV	14.3	4.3 - 38.8

Table 2. Risk factors related to PK-PD

N	Risk factor present (+) or absent (-)			% Non-Response
	low IDV level	high VL	pretreated with PI	
13	-	-	-	8
9	+	-	-	11
11	-	+	-	9
5	-	-	+	20
9	+	+	-	56
6	+	-	+	50
4	-	+	+	100
8	+	+	+	100

Table 3. Variability in IDV PK in children

AUC (mg/lh)	Dose (mg/kg MW/d)		
	100 (n=19)	150 (n=17)	200 (n=5)
<10	42%	12%	0%
10-30	53%	76%	20%
>30	5%	12%	80%

Burger et al., 1st Intl Workshop on Clinical Pharmacology in HIV Therapy, Noordwijk, 2000

shown by Gatti and colleagues in a group of 11 children (aged 9-13.6 years) given indinavir at 500mg/m² TID. AUC and C_{max} levels in the children with and without renal side effects were 53.6 vs. 30.2 (AUC) and 15.3 vs. 9.8 (C_{max}) respectively. [2]

Nelfinavir can produce similar PK difficulties, and this was shown in a recent presentation from the ATHENA study. After a median follow up of eight months we had about a 30% virological failure in a group of 48 treatment-naïve adults using nelfinavir 1250 mg BID. If a patient has a relative concentration below 0.90 (ie 90% of the average data) we saw 50% failure in that patient population, whereas there was only a 17% failure in patients with higher drug levels. The relative risk in this group was 3.0. [3]

Using this threshold of 0.9, we also analysed the sensitivity and specificity necessary to predict whether a patient will fail therapy. We determined this to be 64% sensitivity and 75% specificity, which may look low for a diagnostic test. However virological failure is multi-factorial and there are other important factors such as adherence to consider.

Table 3 shows the relationship of dose to concentration in children using indinavir and interpatient variability in pharmacokinetics with Pls. [4] Of the nineteen patients who received the same dose, in this case 100 mg/kg metabolic weight, only 50% came within the target range of AUC - with 40% below and 5% above. This variability in indinavir pharmacokinetics can be partly explained by the age of the children. Drug clearance reduces with age. It therefore appears that you have to increase the dose even more in the youngest children even when correcting for metabolic weight.

What about sampling times?

There are several important aspects for TDM that I would like to raise. Although it is reasonable to look at trough levels if you are looking at virological efficacy, it is important to realise that the trough level is not always the C_{min}. After taking medication the drug level continues to decrease for the next 1-2 hours. There may also be some variation between trough levels in the evening and morning.

The lower quantitation range of assays can also be less accurate than in the middle or the highest range - so that is a problem in doing only trough levels. There are also practical issues with the patients coming to the clinic for a pre-dose level, which makes accurate recording of timing of the previous dose so important. Only if it is twelve hours (+/- 1 hour) for a BID regimen can you use it for a trough, or C_{min}.

To check toxicity levels in children you will need to check the C_{max}. The time for sample for this will vary from 1-4 hours depending on the T_{max} for individual drugs. It may be rational to do a pre-dose concentration but what is actually the C_{max}?

In both cases, the best thing to do would be a full PK curve to determine the AUC and all the other parameters. Although this is not possible in every situation, we do this in Holland for every child who starts treatment.

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Case studies

Case study 1

The first example is of three children that started treatment with a triple drug combination including indinavir. [5] They all had a good virological response but after one year they relapsed. Their indinavir trough level at that time was <0.1 mg/L. We clearly thought that the low drug level was the reason for the relapse and so we intensified the treatment in these three children by adding a low dose of ritonavir to boost the pharmacokinetics.

The effect of ritonavir in this situation was quite variable with indinavir drug levels increasing to 0.24, 0.7 and 1.9mg/L, but this addition of ritonavir was sufficient for viral load to become undetectable in all three children. This is clearly a way of effective intervention when you see low drug levels and when you see virological failure.

Case study 2

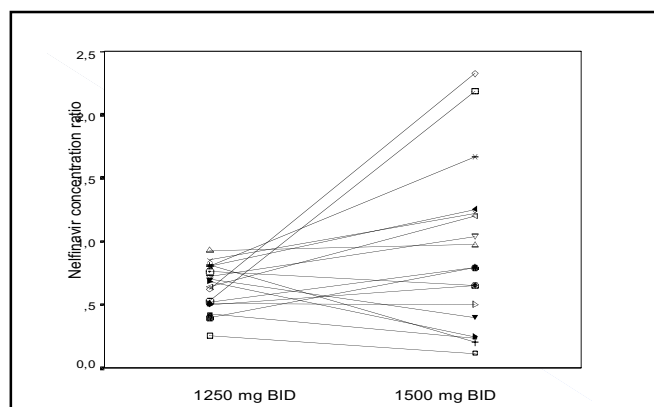
The second example is of adults who suffered from urological symptoms when they were using indinavir 800 mg TID. All these patients were found to have indinavir drug levels that were at least double the expected level. We felt confident in decreasing the dose to 600 TID. We reduced the indinavir concentration ratio to around 1.0 (0.63 – 1.37) - which is considered normal. Subsequently the patients all remained free of symptoms and maintained undetectable levels of viral load without future rebound. [6]

Case study 3

The last example is from eighteen patients using nelfinavir dosed at 1250mg BID who showed low nelfinavir plasma levels. We increased the dose to 1500mg BID - adding one extra tablet in each dose, but we saw a very variable response - see Figure 4.

About 50% of the patients had a big increase in their drug level, some remained stable and some inexplicably even went down. Although this intervention did not help all patients, at least half benefited from better levels.

Figure 4. TDM intervention to increase nelfinavir dose in 18 patients with low plasma nelfinavir levels



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Drug Level Monitoring in the UK

Saye Khoo



In spite of compelling evidence for the benefits of TDM, and a world-class site at the University of Liverpool, only 2.5% of patients using antiretrovirals in the UK actually get TDM at the moment (including a very tiny number of children). Which is very small indeed compared to Holland or France.

Many doctors who believe that there are definite clinical benefits from TDM - and the evidence is compelling but falls short of being conclusive - often fail to use it as a regular clinical tool. Even if you accept that there are benefits there can be practical problems with choice of sampling strategy and how you define your therapeutic index and these vary slightly from lab to lab as well.

There are at least five different strategies that are used:

- i) full drug exposure (AUC=Area Under the Curve)
- ii) trough level (the concentration at the end of the dosing interval)
- iii) both peak and a trough
- iv) population based pharmacokinetic approaches such as the concentration ratios used in the Dutch Athena cohort, or
- v) more sophisticated PK modelling.

Most people regard measuring AUC as the gold standard. Indeed some of the best data relating drug levels to actual virological response are based on AUCs. The problem with the AUC is that it is quite laborious, difficult and expensive. So a lot of people use trough levels.

In Liverpool we have found that while the trough level gives you an indication of the AUC it is not as reliable as we would like, especially when there can be a lot of variability in the trough levels within the same patient on different days.

This variability in trough results is often due to an inaccurate recording of when they last took their medication. Coming to clinic itself is very disruptive for taking a trough. You have got to wait for the doctor, wait for the nurse, wait for someone to find a vein, and you may be twelve to fifteen hours since your previous dose. This is particularly true for children (who go to bed early, and where dosing may be more erratic), or people taking TID regimens (where trough levels at 6 or 7 o'clock in the morning does not easily lend itself to accurate sampling for

TDM). Nevertheless, trough levels are important especially in relation to the IC50. We therefore use a trough and the peak 1-2 hours later to reduce some of the variability. This doesn't get round the problem that troughs can be difficult. They require training of both patients and clinic staff to take the bloods at the right time. Current clinics in the UK operating from 9am-5pm do not lend themselves to accurate TDM.

Various programs have been developed to allow full mathematical modelling. This can be performed from a sample taken at a random time point, with knowledge of the patient's exact dosing times for the past couple of days. From this one sample you can derive the AUC, the Cmax and Cmin, and the clearance for that patient. Although this approach is in its infancy this is probably the way forward. The difficulty of this approach is that you need different models for each combination of drugs, even when the same drugs are being used. The addition of ritonavir to indinavir at different doses (ie 100/800, 200/800, 400/400 etc) requires separate models because different doses of ritonavir have a different effect on indinavir clearance.

In the paediatric setting there is an additional problem because of different metabolic rates at different ages. Neonates may not clear PIs well but metabolic function is increased during infancy (to levels greater than that of adults) and this increased clearance may result in infants being under-dosed. Depending on the drug involved, metabolic function may approach that of adults by around 2 to 6 years. A large amount of data are required to build these different models, but much of this information is already available from different labs and industry, and we need to get together to pool this data.

In the UK, TDM is largely done through the website at the University of Liverpool. We offer a service for PIs and NNRTIs. Although the uptake has not been as great as in Holland or France it has been steadily increasing over the last 18 months. At the end of 1999 we were doing roughly twenty requests per month. This rose throughout 2000, and may have in part been

Figure 1. Uptake of TDM service in the UK

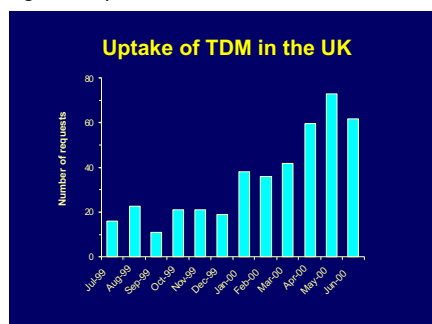


Figure 2. Frequency of drugs requested

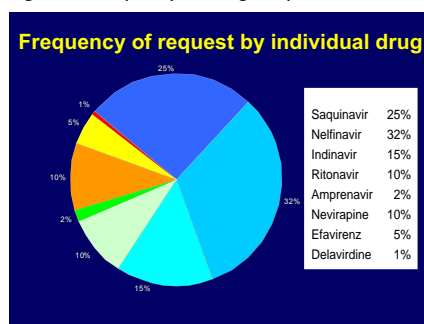


Figure 3. Reasons for requesting TDM

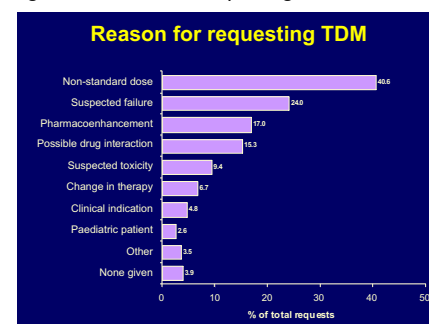


Figure 4. Sub-therapeutic troughs

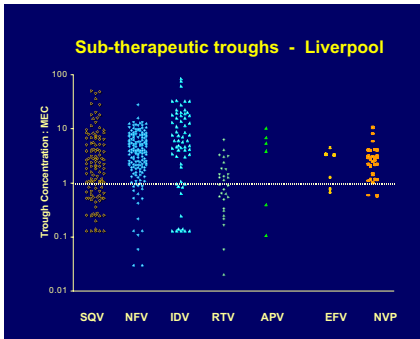


Fig 5. Compared results from 3 TDM cohorts

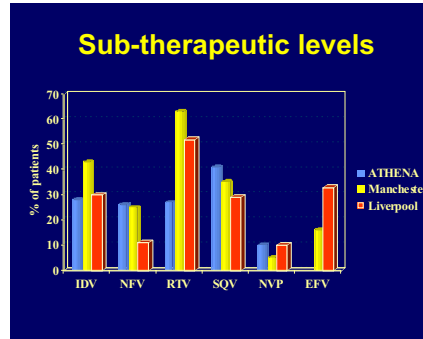


Figure 6. Results and recommendations

	Nelfinavir	Saquinavir
Adequate (no action required)	75.8%	50.4%
High (repeat TDM / dose modify)	5.9%	6.8%
Low (repeat TDM / dose modify)	15.0%	34.6%
Wrong time/type of sample	2.6%	5.3%
Insufficient information	0.7%	3.0%

due to funding for TDM from industry (Roche with saquinavir and nelfinavir, and Merck with indinavir). Indications for TDM include altered liver function, PI plus NNRTIs, potential drug interaction and all paediatric patients. We currently receive over 80 requests per month and the majority of PIs analysed are saquinavir, nelfinavir and indinavir.

The most common reasons for requesting TDM are shown in Figure 3, and include use of a non-standard dose (40%). This is a very broad kind of definition of people who maybe had TDM done before and had insufficient levels which we have increased. It includes people who are on two PIs, or PI plus NNRTI, or anti-tuberculosis chemotherapy. PK enhancement with ritonavir accounts for 17% of the requests.

The next most common reason for seeking TDM is suspected treatment failure at 24%. You could argue that this is shutting the stable door after the horse has bolted, but certainly if you do it early on enough, or have the results of resistance testing, TDM may offer the option of treatment intensification (e.g. by increasing sub-therapeutic doses, or boosting with ritonavir). Understanding why a treatment failed is also essential if you are to prescribe an effective subsequent regimen.

The other reasons are fairly standard - suspected interactions or toxicity, and clinical indication, for example for people with hepatitis C co-infection or liver impairment. I had a patient who had a liver transplant about two months ago and prior to his transplant he was clearly not clearing efavirenz at all. We used TDM to find his optimal efavirenz dose which turned out to be as low as 200mg twice a week. This is one situation where TDM was essential for clinical management.

You will see that only a small amount of our work is with children. This perhaps largely reflects the relatively small cohort of children in the UK, but also the general uptake of TDM. Only 2.5% of the 12,000 patients in the UK who are on antiretroviral therapy actually get TDM at the moment, and compared to France or Holland this is very modest indeed.

Figure 4 shows pooled data from Liverpool suggesting that a substantial proportion of patients have sub-therapeutic trough levels of PIs. It is also worth pointing out our cut-off for both saquinavir and nelfinavir are much lower than in many European labs. Some people considered that ritonavir-boosted combinations would obviate the need for TDM. We found that when used with saquinavir or indinavir, ritonavir definitely elevated the plasma levels of those drugs, but that there were still patients who failed therapy.

Figure 6 shows data on sub-therapeutic levels from three different cohorts. The left-hand bars relate to the Athena Dutch cohort which includes 300 - 600 patients using

concentration ratios and was presented by David Burger at Noordwijk in March 2000. The centre bars are from a study that Liverpool University has recently been involved with in Manchester. These are data from the first 50 of about 180 patients taken from random time points in an unselected clinic cohort, and using mathematical modelling in collaboration with Virco to derive the estimated trough levels. The right-hand bars are taken from trough samples sent for TDM to Liverpool. The Liverpool cohort may represent a selected group of patients who are most at risk of failure, but this bias was not present in ATHENA or the Manchester cohort.

Each of these three different methods in different cohorts has produced roughly comparable results. The high frequency of low ritonavir levels largely relate to 'baby' doses which haven't been excluded yet from the analysis. Around 30% of indinavir samples are sub-therapeutic (even with ritonavir), and 12-24% of nelfinavir, 30-40% of saquinavir, and 10% of nevirapine samples also fell below therapeutic levels. These kind of data are very worrying, and somewhat depressing given the high numbers of people who are working through an already limited number of treatment options each year. There is clearly a substantial number of patients not getting enough drug in their system to suppress even wild type virus let alone their own isolates.

Finally, although we give out advice with all drug levels we have no idea whether doctors chose to follow this - and that is clearly important information to know.

Individualised TDM is recommended for all children currently using PI or NNRTI-based antiretroviral combinations.

For further information on drug level monitoring please contact Sara Gibbons, Saye Khoo or David Back at Liverpool University. All costs for patients using saquinavir, nelfinavir or indinavir combinations are covered by the subsidised programmes supported by Roche and Merck.

A copy of the TDM request form for this service is included on page 40 of this report.

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A call for resistance testing...

Polly Clayden

Resistance in children and its association with virological failure was highlighted in two studies presented at the recent Retrovirus conference in Chicago. Another study from Lisa Frenkel's group revealed that, as we're seeing with adults, having the M184V/I (3TC) mutations, could also offer some benefit to children in salvage therapy.

Although there are still persistent question marks concerning the clinical use of both genotype and phenotype resistance testing, for adults these tests are now integrated into the standard of care in Europe and the US. [1, 2] They are also available for children in some countries. Dr Schmidt's group from Germany examined the incidence of resistance in their group of children, and took the unusual step of comparing the results to those obtained from an adult cohort [3].

Virological treatment failure appears to be more frequent in children than in adults, and the authors highlighted the following reasons - adherence to therapy seems to be more difficult, different pharmacokinetics may result in subtherapeutic drug levels, viral load is generally higher in children than in adults and the antiviral CTL response is less efficient in the first year of life. Since information on the prevalence of highly resistant viral strains may influence current guidelines for diagnostic and therapeutic management of children, their aim for this study was to evaluate drug resistant profiles in paediatric HIV infection.

Genotype and phenotype tests were performed on 46 samples from 35 children - age 2 months to 16.5 years (median 8.4 years), at the time of their first resistance test. Detailed drug histories were available for all the children. This revealed 15 (42.9%) of the samples to be resistant against one group of antiretrovirals, 13 (37.1%) against two and one sample (2.9%) against all three classes. 11 follow up samples were obtained from 9 children and in 7 cases resistance had increased. 5 samples including 2 follow ups showed nucleoside multi-drug resistance. Results were then compared adult samples to analyse the frequency of key mutations.

Nucleoside multi-drug resistance was found to be more frequent in children than adults in this study. They believed that this was explained by the past (and sometimes current) common practice of using dual nucleoside therapy for children, which is no longer the standard of care for adults. In addition this was also likely to be provoked by insufficient suppression of viral replication, which appears to be more frequent in children than in adults. The investigators found that NNRTI and PI resistance was lower in children than in adults, although they speculated that, 'A higher frequency, *may only be a matter of time* as suggested from the increase in resistance in most of the follow up samples'.

They explained that, although HIV infection may differ considerably between children and adults in its biology as well as treatment, and that this paediatric cohort may not reflect a standard population, however 'relevant information may be extracted from the comparison of paediatric and adult resistance profiles because reasons for resistance testing were

identical for each group'. The investigators concluded that 'since resistance testing recently proved to be beneficial for the management of adult HIV infection, the prognostic relevance of geno and phenotypic resistance testing should be prospectively analysed for optimising therapy in HIV-1 infected children.' This study was aptly titled 'A call for resistance testing.'

Dr Susan Eshleman's group analysed resistance in children experiencing virological failure from the PACTG 377 [4]. In this study experienced children were randomised into one of four treatment arms using different combinations of d4T, 3TC, nevirapine, nelfinavir and ritonavir. Children were screened at baseline and at treatment failure.

Amongst their findings they reported that the selection of nevirapine mutations was far less common among children receiving 4-drug nevirapine containing combinations. They also found that although nelfinavir and ritonavir resistance was rarely detected at the time of failure, mutations associated with these drugs as well as additional 3TC and nevirapine-associated mutations were frequently selected in children who maintained their initial study regimen after virological failure.

Finally to end on an optimistic note, Dr Lisa Frenkel and colleagues reported a beneficial effect for children in having the M184V/I mutation at baseline prior to starting salvage therapy in the PACTG 366 trial [5]. Children with and without the M184V/I mutations were evaluated for their response to a new regimen 4-drug combination. Regimens were dictated by their prior use of PIs and/or NNRTIs and included at least 2 agents that they had not used previously. Children having the M184V/I mutations had a greater chance of achieving undetectable viral load both at weeks 12 and 24. They concluded that 'the M184V/I mutations may have a clinically beneficial effect in the suppression of viral load during salvage therapy.'

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Comments from Clive Loveday and Stephane Blanche

Clive Loveday...

How critical are resistance assays to routine management in children's care?

The arguments are the same as for adults, and personally I have no doubts that resistance testing is fundamental to effective patient management.

But do we have scientific evidence that resistance testing will support patient care?

In adults I know of about 8 or 10 trials to evaluate resistance testing – Viradapt, GART, NARVAL etc, and one year ago I had no doubts. I was confident that trials would generate enough evidence to support their routine use.

Now I think that I probably underestimated the role played by drug levels and adherence (both of which can be particularly hard to achieve with kids).

So do we need another randomised, controlled trial?

Certainly with adults it would probably not be possible to set up another one, because the tests should now be more widely available anyway.

We've leapfrogged ahead, but as far as real, convincing evidence is concerned we're not really finding a massive difference between using and not using genotype testing - so far we haven't shown significance greater than 0.05.

To make the best use of resistance testing it is crucial that we include drug levels and adherence. A lot of people pay lip service to adherence, but I know that I for one can never successfully take medications for even a couple of weeks.

It is essential to realise that it is not possible to expect resistance testing to make a significant difference in isolation. It is only one of three critical factors, all of which need to be followed.

As far as kids are concerned, although, on one hand I think testing is vital for kids and when samples are sent down to me I do them, I must make a plea for randomised controlled trials. So I am keen to see PERA go ahead, we need at least one trial, we've got to get convincing evidence for children.

Have you heard any particular arguments against resistance testing for kids?

One reason why kids might not be getting resistance tests is because some would argue that, because kids have a more limited choice of drugs available to use, there's little choice after each failure. You could reverse it though and argue that

there's all the more reason to give each treatment the best possible chance of working.

Are there significant differences from the point of view of evolution of resistance with kids?

From a virologist's point of view, the development of resistance is exactly the same in children as in adults. If you don't get enough drug concentrations - either because of PK or non-adherence – you will get the evolution of resistance - regardless of someone's age.

PENTA 5 produced some ambiguous results. Resistance was certainly slower to evolve, but kids have higher viral loads. The virus certainly can't be different but perhaps the way that the virus is handled is. The only explanation I can think of is the virus is being cleared more slowly - it can't be that replication isn't fast.

But kids get resistance just the same as anybody else; there's no doubt about that.

Stephane Blanche....

What is the situation with resistance testing for children in France? How many, for example have been done at your hospital?

Genotype is recommended for children exactly as it is for adults.

More than 100 tests have already been done at the Necker (Necker Hopital Enfants Malades), and analysis is underway, including a global comparison with adult data.

My feeling is that genotype is certainly more important for children, since virological failure rate is clearly higher than in adults. For PIs and NNRTIs the answer is nearly always the same. Resistance is nearly always found if these drugs have already been used. So it's not extremely useful.

However for nucleosides the pattern is extremely variable and probably useful for re-cycling old molecules.

Genotyping is also clearly recommended for newborn babies...

For newborns, genotyping is systematically done but in this case it is not so useful since all our infected babies are from mothers who were not treated during pregnancy.

As it is a very small number of cases I think it is reasonable to continue to test them anyway.

Roundtable Discussion

The Role of Treatment Interruptions?

Moderators: Di Gibb, Stefano Vella

Despite a great deal of interest at the moment in STIs as a part of adult care, so far no research has been done into possible use of these strategies in paediatrics. Stefano Vella is involved in a large Italian STI study in adults, and the PENTA group are currently discussing studies for children in Europe.

Di Gibb: We are discussing the possibility of doing structured treatment interruption studies in Europe within PENTA.

Guidelines from the US, for treating children early during primary infection, have been adopted quite widely, but until now we haven't really thought about stopping treatment in these kids. In some of the adult trials the set point was lowered after stopping treatment in primary infection, but we are concerned that children will not develop a similar HIV specific response.

A second point is that, because children's CD4 counts increase better than those in adults during HAART, we may have some room for doing structured treatment interruptions even in chronic infection.

Stefano Vella: I am not a paediatrician but these are interesting points and you are looking at primary infection if you treat children after birth. I don't know how they compare to adults and I'm not sure about when children should stop treatment.

Lisa Frenkel: I think that in support of stopping, all of us have heard cases of tremendous CD4 recovery which have prompted a discontinuation of treatment. And we have several children who have now been off treatment for more than two years and lost hardly any CD4 cells. This may be to do with thymic reserve, which will be much better in kids. Instead of the 4-7 years that adults take to progress to AIDS maybe these kids would take 10 years. This is another reason why they may be room for the trials in children.

Stefano Vella: And the reasons that we have structured treatment interruptions for adults - to do with quality of life issues are even more important in children's lives.

Question: Stefano, why don't you include children in the new Italian STI study?

Stefano Vella: I think we need to have data before we start with kids, and I think it needs to be done by paediatricians.

Di Gibb: It should be in parallel...

Stefano Vella: Maybe,

Stephen Arpadi: I am going to play the sceptic. Franco Lori's experiment in monkeys presented at ICAAC showed significant differences between interruptions in acute versus chronic infection. In acute it works very well, but in chronic it does not.

Another issue is related to informed consent. Do you think you can randomise children into arms that are so different. How do you control for people entering a study who may strongly

prefer the interruption arm or into the standard of care?

A third point is that we think that the immune system of children is very naive, and allows a lot of manipulation. But if we think of something as common as PCP - a glycoprotein antigen - if you don't link with a protein you don't induce immunity if you are younger than two years of age. So we have a very plastic immune system with the potential for recovery, but we also have limitations.

Ronald de Groot: I would also like to add a caution. In Europe the number of children available for studies is very low, if you want to study this in a structured way. If we look to the results from current studies, for example from the lopinavir/r trial where 70% - 75% of the children still have viral loads below 50 copies after a year. It may not be very promising prospect to propose a study because there are too few people to study.

I would suggest that we need a different approach. We hear a lot of important clinical observations, yet these observations are not put together in a structured way. I don't think that we are ready to go ahead with this in a paediatric population. I would like to see what the results in the adult population are first.

I would like to see better controls and data on the patients who fail (for whatever reason) and who are not on therapy. We need to know what happens to these patients - we want to know what their CD4 counts are, how their viral load changes, and what are clinical barriers. We should be looking to develop a registry of all kids with HIV - not so much because we are interested in another study, but because we are interested to see how any individual child responds in a situation where they are off therapy.

Di Gibb: I think it would be very hard at this moment to include children in treatment interruption studies because so few children currently get persistently low viral loads. This may make it difficult to know whether increases in viral load are necessarily due to the treatment interruption rather than treatment failure.

Lisa Frenkel: I must emphasise that I am only interested in children in this context who have had an excellent treatment response. I am thinking specifically of children whose CD4 count has increased from under 100 to over 1000 cells/mm³. They have now been successfully treated for a certain period of time. How will they do if they stop? Certain children have stopped and they have done extremely well although we don't understand the immunological basis of the response.



Are there questions from the audience?

Question: This is a comment rather than a question. My first thought about doing these trials in a paediatric setting, is the difficulties we have with adherence in adults and stopping and starting. It can be difficult for adults when they have to restart having stopped - and may this be even worse for children?

Stefano Vella: We had this problem regarding stopping and starting in adults when we talked to our colleagues and community organisations. Many were not so concerned about this as it could actually increase adherence if it is carefully explained. The advantages of a drug holiday are as appealing to children as they are to adults - you can say that if they behave very well in these three or four months – they can then have a period without treatment.

It is important do this in the context that clearly explains they will have to start treatment again later though. Some of the adult patients found it difficult to restart 'lifelong' treatment after they experienced how good it was to stop. If you tell them that they have to start again but then you may also re-stop again later - it is a better perspective and it works. The long-term perspective is to study this over ten or twenty years.

Because the response to therapy has been so effective, we now have to think of treating patients for much longer, and this is a strategy to make this more possible. Because I have heard of data, for example, about the toxicity of therapies that accumulate. Even with the best drugs available, it may not be possible to avoid the accumulative toxicity after even four or five years. I would prefer to have cycles with the good therapies.

Ronald de Groot: One of the core issues with treating children is adherence – and it is an area that I don't think we are doing very well. Although in the Netherlands we see children every week, or even more frequently when they start treatment, we then go to a regimen where we might see them only once every three months.

After a year or two we increasingly see kids who, despite all the efforts of the physician and the HIV nurse and the social worker are still not adherent. We use pill boxes and other support material but still we don't do well, and we need to pay much more attention to the social science aspects of HIV care. We need to be able to estimate which children are at risk of non-adherence. For example, we use questionnaires before starting treatment with these kids to get an idea of their social background and social support in the family. We hope that this

will give us information, which we can link to failure in the long term so we can know which populations need special approaches.

Maybe one visit every three months is not sufficient, maybe we need to see them every four or six weeks. One home visit is not enough for many people, maybe we need more intensive consultation with parents and children. I think that this is a major factor behind the results and we need to deal with adherence before even talking about triple therapy or quadruple therapy or treatment interruptions.

Question: We can measure glucose levels quite quickly in blood with a 'pinprick' test - how far do you think we are away from this for measuring drug levels?

Ronald de Groot: I think we are still far away from that. We use HPLC methods that we developed ourselves. There is not one commercial company that is developing immuno-assays, so unfortunately I think we are many years away from that.

Question: Is it possible that children may do better with adherence than adults because their mother gives them the drugs, and also with treatment interruptions?

Di Gibb: There are a lot of complicated issues related to adherence in kids. For example, if mothers are HIV-positive themselves, it depends which treatments they are on and what they think of their own treatment. They are certainly not going to want to give something to their children that makes them feel dreadful.

Children also are getting older - in the US now almost a quarter of kids are going into adolescence and we are not that far behind in Europe. You then have all the issues of adolescents starting to take their own therapies, which involves developing new approaches again.

For structured treatment interruptions we need some parallel trials in children. If we wait until we get adult results, everyone will be doing it in a chaotic way anyway. Also, the answers may well be different in kids because of their developing immune system. Maybe we can think of situations where we stop for longer periods of time and restart based on falling below a certain CD4 count. That might be a useful trial design.

This could help adherence because you can explain 'if, your CD4 count has dropped below this level you need to restart'.



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So it is not just stop and start in a vacuum and I think that would be a good idea for kids.

Question: Could you address the particular issue of hypersensitivity reactions, and using drugs that require dose escalation regimes in structured treatment interruptions.

Stefano Vella: This is a good question. We don't include patients on 'triple nucleoside' therapy because this invariably includes abacavir and this is a risk. We might also need to exclude abacavir, even in terms of background nucleoside therapy. There is a risk of the person stopping treatment while they are having a mild hypersensitivity reaction that hasn't been noticed. Restarting with abacavir is contraindicated and can be very dangerous. It is a question of being very careful in monitoring patients while they are on therapy to catch any early signs.

Question: I think there is a place for structured treatment interruptions in children and perhaps this will lead to a better response. I am wondering about the immune activation when you have viral rebound. Are there any approaches to suppress immune activation during a period without drugs?

Stefano Vella: It may be possible to do something during the interruption or just before. At the beginning, for example, one possibility would be to decrease immune activation and so incur less damage. Another strategy could be to use IL-2 before stopping - but we didn't want to add this complexity to the trial. If you have a large viral rebound and a greater number of CD4 cells ready to be infected, this could lead to further damage – although I know that this is an approach in the UK.

Octavio Ramilo: I would like to raise the issue of salvage therapy in people who have very high viral load and resistance to existing drugs - and the risk of having large drops in CD4. I know two people - one adult and one child – who then had practically no CD4 count left after a long treatment

interruption. It was very hard for them to maintain the new therapy when they restarted although I am pleased to say that after several months they saw the CD4s increase again.

Stefano Vella: In some patients it works but I am scared that it may only work for a short time. When wild type virus returns it drives the CD4 decrease but I also think that resistant virus will return later, possibly in only a few weeks, although we don't have data from sufficient studies.

Lisa Frenkel: This is definitely an area where we need trials. The treatment results presented by Veronica Miller who used mega-HAART after a treatment interruption, and the data from Julio Montaner who used mega-HAART with no interruption, both look very similar to me.

I think you get a CD4 loss with the treatment interruption, but the exact mechanism from the benefit of mega-HAART is not known. Because there can be so many different sub-populations the virus that is resistant to all the different therapies may only be minimal. It is the people who don't have viruses with good fitness that are resistant to all the different elements of mega-HAART that I think are the main responders. There are diverse and strident opinions about the use of STI for re-sensitisation of the virus to previously resistant drugs, but I, like Stefano, don't think that is the mechanism.

Di Gibb: Are you suggesting we should be doing trials in heavily pre-treated children, like the one that Octavio was describing, because I don't agree with this. You may stop treatment for a while for other reasons – because they are so fed up, or you think that a break will improve adherence in the subsequent regimen, but I am not sure I want to randomise them to stop and watch and wait for some response.

Lisa Frenkel: I would like to see the people who are believers in treatment interruption for re-sensitisation look at it in a more objective way and there is therefore theoretical room for trials.

Immune reconstitution in children

Annemarie van Rossum

This Dutch study gives a very clear report of the extent to which HAART is capable of reconstituting the immune system of children, regardless of their age or the stage of their HIV.

In this Dutch study we examined the extent of immune reconstitution in a group of HIV-infected children after initiation of HAART [3]. We found that children with HIV-1 infection have a greater capacity to reconstitute their naive CD4+ T-cells when compared to HIV-infected adults treated with similar antiretroviral therapy.

This is not an unexpected finding, since naive T-cell recovery is believed to be thymus-dependent and thymic function diminishes with age. Previously, age was reported to be the best predictor of the rise in CD4+ T-cell numbers and naive T-cell numbers after initiation of antiretroviral therapy in HIV-1 infected children. CD4+ T-cell numbers in HIV-infected children on HAART recover more rapidly than CD4+ T-cells in HIV-infected adults. However, it is still unclear to what extent the immune system of HIV-infected children is capable of normalising, since data on long-term immune reconstitution in HIV-infected children on HAART is not available.

In a considerable number of HIV-infected adults treated with HAART, CD4+ T-cell numbers stabilised or even slightly decreased after 1.5 years of therapy, sometimes without having reached normal levels.

In this study we evaluated immune reconstitution in a group of children treated with one protease inhibitor and two nucleoside reverse transcriptase inhibitors over a period of 96 weeks. Changes in the number of CD4 and CD8 cells and their naive and memory subsets were analysed and compared to normal paediatric age specific reference values.

71 children were enrolled (age range 1 month - 18 years) in two prospective, open label, uncontrolled studies to evaluate their response to PI-containing HAART regimens of either indinavir/AZT/3TC or nelfinavir/d4T/3TC. Entry criteria included antiretroviral naive or nucleoside-experienced children, with viral load values above 5000 copies/mL or CD4 counts below the lower limit of age specific normal reference values. Blood samples were taken weeks -2 and 0 before HAART was started and throughout the 96-week study period (at weeks 1, 2, 4, 8, 12, 24, 36, 48 and 96). Lymphocytes were phenotyped as CD4 and CD8 T-cells, with naive and memory subsets. Relative CD4 cells were calculated in relation to the median age-specific reference values. Virologic responders were defined as those who either reached undetectable viral load (<400 or <500 copies/mL) or achieved and maintained (throughout the study period) a >1.5 log drop by week 12.

Analysis revealed that both the absolute CD4 count and the CD4 percentages increased significantly ($p < 0.001$) from a median of 471 cells/mm³ and 17%, to 939 cells/mm³ and 32% respectively after 48 weeks. In all age groups the increase of total CD4 cells was caused by an increase of naive CD4 cells. A

tendency towards an inverse correlation between the increase of absolute naive CD4 cells and the age range of children was observed at 4, 24 and 48 weeks ($r = -0.31$, $p = 0.03$; $r = 0.34$, $p = 0.02$; $r = -0.47$, $p = 0.01$; and $r = 0.33$, $p = 0.04$ respectively).

When CD4 cell restoration was evaluated as a percentage of normal values however, an inverse correlation between the increase of naive CD4 cells and age was only observed after 48 weeks ($r = -0.41$, $p = 0.02$). Although younger children produce more CD4 cells in absolute numbers, they require relatively more CD4 cells to catch up and normalise their CD4 counts. It was concluded therefore that older children are able to normalise their CD4 counts equally as well as younger ones.

The investigators also found that, although strongly immunosuppressed HIV-infected adults experience poor immune reconstitution, children with lower baseline CD4 counts showed a greater increase of CD4 counts and recovery to normal values after the initiation of HAART. They were also surprised to find that children defined as virologic non-responders still benefited from HAART and showed no difference in immune reconstitution at any time-point than those defined as virologic responders.

Overall we concluded that, these results indicate that immune reconstitution in HIV-infected children is independent of their age, suggesting that children's thymic function enables all age groups to restore their different CD4 production demands. We observed a more rapid and complete immune reconstitution than would be expected in adults, even in children with advanced HIV-infection. Remarkably, HAART had a beneficial effect on immune reconstitution regardless of virological success.

Reference:

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Annemarie van Rossum is paediatrician in training, Department of Paediatrics, University Hospital Rotterdam/Sophia Children's Hospital. She is currently working on a PhD thesis on the treatment of HIV-1 infected children enrolled in a Dutch multicentre trial. Her interests are clinical, pharmacological, immunological and virological aspects of HIV infection in children.

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Salvage therapy

Grace Aldrovandi interviewed by Polly Clayden

Multi-drug regimens, using more than three drugs, may be even more important for children than for adults - especially when they have developed resistance to existing drugs. Grace Aldrovandi is currently running a trial using mega-HAART in very drug-experienced kids – PACTG 1007.

Before setting up this trial, how long had you been treating kids with multi-drug therapy like this in your regular clinic?

We first began over three years ago. Kids were coming to us very heavily pre-treated and resistant to everything with viral loads in the millions and CD4s of nothing.

So you were troubleshooting well before mega-HAART gained currency as a term?

Yes, it was pretty similar to what Montaner was doing with adults - he started because his patients forced him to try this as a last resort.

You compare heavily pre-treated children with HIV to multiple-relapsed cancer patients, and therefore use very intensive therapy. Was this considered a very radical approach?

Everybody thought I was joking, but I thought it made sense. I've always been intrigued with how leukaemia was cured in the early days. I was fascinated by the relationship between dose intensity and success - if you use too few drugs and/or a lower dose of chemo, you still get a similar initial response to treatment, but only for a limited time.

For example, children with acute leukaemia who received 94% or less of their chemo were more than five times more likely to become ill again in the future than those who received 99%. A similar relationship between dose intensification and long-term success has been seen with breast, colon, ovarian and many other types of cancer. When lower doses, or fewer drugs, have been used to avoid toxicity rates, there is a drop in the rates of people who are cured.

With HIV, when we get people undetectable, we have got them into a sort of remission. Although some people object to this comparison because they say that people in cancer remission don't have latent cancer, in many ways they clearly do. And although we don't understand what governs relapse in cancer we understand more about it (or think we do) than with HIV.

So using the cancer model, given the higher risk for these kids' to become ill and that this treatment is probably their last and best chance, it makes sense to use everything you've got...

Exactly. It is more difficult to get kids to undetectable anyway because they have much higher levels to start with, especially if they've already used a lot of other drugs. A lot of the data shows that the higher your viral load when you begin each treatment, the more difficult it is to become undetectable.

All your doses are BID, so that gets round difficulty of taking treatment at school, but do you still have major issues with children and adherence?

HIV-infected children are not born in a vacuum and HIV is not the only problem that they and their families have in their lives.

The formulations are horrible, so you can't really blame the children. Plus there is the issue of confidentiality. Unlike a child with diabetes where everyone rallies round to be supportive, a lot of times you don't want your family or other people to know about HIV, so you have to take them into the bathroom and sneak in the pills.

Adherence for children is a big deal, and maybe one of the reasons we have higher rates of detectable viral load in children.

And then, in adolescence...

Not good, they may or may not take their meds. It's very hard for adolescents; they feel that it's very unfair, they worry about their friends at school finding out. They feel very isolated because there aren't that many kids in the same situation and they really resent having to take the medicines. I sit-down and graph out what a viral load does, go through the dangers if it went higher, tell them 'Oh I wish I could take this away...'

Do you find it helpful when children begin to understand what a viral load is and about resistance etc?

I think that it helps. What I do is measure out one millilitre of water and I show them that they have x number of copies of HIV in that amount of blood. I try to explain it that every time you take a pill it's like a bomb that will blast the HIV, I try to make it as concrete as I can.

Sometimes it works, sometimes it doesn't, but I continue to try and educate knowing that it sometimes falls on deaf ears. Part of being an adolescent is thinking you're invincible and it's very hard when you feel well to think that there's a virus inside you that could kill you.

So are there any secrets to getting kids to take all those meds?

I've become more and more convinced that, the thing to do is put in a gastrostomy tube. It can be a psychological barrier for some doctors, but it is much less invasive than a central line which has more complications and which are used routinely. G-tubes are really not that bad, you can remove the tubing and they're just like an extra belly button, nobody needs to know. If my own child needed to take this many pills I would insist on a G-tube.

Most of our children who are that sick are small for their age anyway. So what I tell the moms to do, if anyone notices it in the summer, is just tell them he doesn't really grow too well because he was premature (or whatever), and it's just to give them some food at night. I find that quite do-able and that way you save their mouths for feeding.

For adolescents though, it's a hard sell, but frankly all these teenagers go around and pierce their belly buttons (and

everything else) - if we could come up with a sexy button for them, maybe we could convince them that it's the thing to do...

You've had to make amendments to your protocol because of the pancreatitis risk, what are they?

We lowered the dose of d4T (it was double the standard recommended dose), but we have continued with the ddl and we have now instituted closer monitoring to avoid those risks. We have a bunch of kids waiting to enter in the study when these changes are approved.

I also noticed you are using hydroxyurea...

Yes, so far, but we have to go back to all the regulatory people and of course have very vigilant management and appropriate interventions in cases of any complications. But kids with sickle cell disease already use hydroxyurea.

So as soon as these doses are sorted out, will you resume - it does seem important to know the outcome of this study?

Yes, we look forward to restarting to see if this approach works. Our limited experience, and Montaner's data, would suggest that it does for many but not all.

Our entry criteria are much more stringent than anyone else's and we're taking the children who are the most ill. I don't know of an adult study that has targeted people with a viral load of over 100,000, CD4 counts of under 200 and who have failed as many drugs as these children have.

The data from larger adult trials would suggest that if you are NNRTI experienced you are much less likely to respond, but we'll see. It's really to see if the principle will work. I know that even within paediatrics, a number of investigators have been moving towards five, six, seven drugs, but I think this is the first children's study to look at this.

Do you use TDM to check their levels, this seems particularly important with children?

I am fortunate enough that I have a pharmacologist who does tests here for me. It's not very widely available in the US, but I think it's something that is essential in treating children with HIV, because the levels of drugs in their bodies change all the time. It needs to be done at all times in treatment though, not just in salvage,

Are you seeing lipodystrophy with your kids and other stuff that we're concerned about with adults?

Yes, children on HAART can develop lipodystrophy, lipid abnormalities, and diabetes. The PACTG is developing a study to look at the metabolic effects and the effects on growth of HAART. Anecdotally it appears to occur less than in adults, but it's hard to really say, there's so much more adult experience. I think though, that we may actually get useful answers for adults from the studies in children.

Treatment interruptions (so-called drug holidays) are becoming a popular current strategy for some adults, would you consider this for children, particularly if they were having difficulties with adherence?

Yes, if there are real difficulties with adherence, I have come to the conclusion that no drugs are better than intermittent drugs. At first I was rather scared taking them off treatment, but I have kids off drugs who have maintained stable viral load and CD4 counts.

Do you think that you'll use this very intensive multi-drug therapy more up-front and not just in a salvage setting?

Yes, I would like to start mega-HAART in kids up-front. People

are talking about the whole issue of a latent virus and about intensification but only with one or two drugs.

If you look at the amount of radiation it takes to shrink a tumour... again I think we should learn from the experience of treating cancer and really aim for what's maximally tolerated, and then back off. This should be done in the setting of a study though, so we can answer the question properly.

But there's a lot of toxicity associated with this approach so we need to answer this rigorously and scientifically.

Back to the I007, and by way of a conclusion, can you summarise what this trial will show?

That if we throw everything that we possibly, reasonably (reasonably in quotation marks that is), can at the virus in this very, very, very sick population with resistant virus, can we get anywhere?

If we can't, then we learn that with our present drugs we cannot beat the virus, when it gets to this late stage, and that it's probably not worth subjecting children to all the toxicity associated with this strategy. However, if we can show effect, it means that our weapons (drugs) can still be used to knock the virus down, even after it has won the first rounds of the fight.

I have no doubt that we will have to pay a price in terms of side effects, so that every family will have to decide if the potential benefit is worth the risk. Hopefully this study will provide children and their families with an additional option, which because it is collected in a controlled scientific manner, will be supported by data.

What happens next then, can we then go to a maintenance regimen?

That's what we'll look at next - daughter of I007...

Study summary

Entry criteria

- aged between 7 - 22
- CD4 count less than 200
- viral load over 100,000
- nucleoside, PI and NNRTI-experienced
- previously used nelfinavir and ritonavir for at least 6 weeks

Protocol

- For 8-drugs to be used together: d4T, ddl, 3TC, nelfinavir, ritonavir, saquinavir and nevirapine in higher than usual doses, and hydroxyurea.
- drug levels will be monitored with regular TDM testing
- drugs will be given once or twice a day.
- first two weeks in hospital and have someone visit them at home each day for the next twelve weeks, twice a day, to give them their medicine at first and then make sure they are taking (and being given) them properly.
- Their parent or guardian must give informed consent
- the child must know his/her HIV status and (in states where the law permits), give their assent to participate.
- Children, their parents, and health workers must all believe they can be adherent.

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Side-effects: lipodystrophy in children

Stephen Arpadi



With over 50% of adults on treatment reporting some degree of body shape or metabolic changes, and uncertainty over the mechanism and treatment, this is obviously an area of concern for paediatric care. Steven Arpadi is one of the first doctors to have presented research in this area we were very fortunate that he was also able to attend our meeting in London.

Symptoms of lipodystrophy reported in HIV-infected adults include fat depletion (lipoatrophy) - usually subcutaneous from the face, buttocks, arms and legs - and fat accumulation, usually visceral fat accumulation, but also buffalo hump, breast enlargement, bilateral symmetrical lipomatosis.

The metabolic alterations that have been reported in lipodystrophy include insulin resistance and hyperglycemia, hyperlipidemia and dyslipidemia which includes relative shifts in HDL and LDL and often an additional increase in the total cholesterol.

These lipid and insulin abnormalities which are occurring in the context of HIV are of concern as they are clearly established as risk factors for coronary heart disease.

There are a number of issues that have made the study of these abnormalities problematic. These fat and metabolic disorders are not seen exclusively in HIV diseases; acquired and congenital forms also exist. Also, the fat and metabolic abnormalities that are observed may not necessarily co-exist or be connected. Also while it seems to be the case that many physicians recognize lipodystrophy when they see it, at present there is no agreed objective case definition of 'lipodystrophy'. Evaluation of the sensitivity and specificity of patient self-reported body shape changes is also rather limited.

The estimated prevalence of these various, either individual or combined, body shape changes vary widely depending on the population of study and the criteria used. In a recently published review, Grunfeld suggested the prevalence of abnormalities may be as high as 83% in treated HIV-infected adults. [1] These body shape changes have been reported in men, women, various racial/ethnic groups, different geographic groups, and now we have data indicating the occurrence of fat abnormalities in children as well.

Lipodystrophy and children

Data is very sparse with regard to lipodystrophy in children. A survey performed by Babl and colleagues reported a prevalence of 1%, of physician assessed body fat distribution abnormalities across the US paediatric Aids clinical trial units. [2] There have also been case reports of lipodystrophy including hyperlipidemia to levels warranting intervention in children with PI use. [3, 4, 5]

We observed a nine year old whose parent reported concern about an increasing abdominal size about nine months after

beginning a new therapy. This patient had also been a subject in a prior study of body composition performed initially to study growth failure and wasting in children, so a baseline Dual-X-ray energy absorptiometry (DEXA) scan was available for comparison.

During the 18 months between studies, (about nine or ten months after beginning his new regimen) the child had a normal growth velocity. Despite a weight gain of 3.5 kilos there was a loss in body fat of approximately 0.5kg. Given his increasing weight this represented about a 5% drop in terms of percent body fat. We saw loss of fat in his arms and in his legs - lipoatrophy - with increasing amounts of truncal fat. Intra-abdominal fat was assessed by means of a total body MRI and was found to be markedly increased. This boy also had elevated cholesterol and triglyceride levels.

After the age of five, indices of central fat in children are relatively stable and changes in the subscapular: triceps subcutaneous fat ratio doesn't change significantly again until after the onset of puberty. This makes this middle-age of childhood an ideal time to study these types alterations in regional fat distribution.

We recently performed a study to evaluate the relationship of regional fat re-distribution and levels of triglyceride (TG) and cholesterol (CHL) in an longitudinal observational clinical cohort of 28 prepubescent vertically HIV-children. [6]

DEXA, random triglyceride and cholesterol levels, PCR RNA-viral load and lymphocyte subsets were analysed at baseline and follow-up. Between and within groups differences were assessed using OR and Fisher exact test for associations. Lipodystrophy was defined as requiring both a decrease in peripheral fat (arm and leg) and an increase in trunk fat, TG and CHL were compared to expected normal values from the US National Child Evaluation Programme.

The mean age was 7.5 years old (± 2.3 , range 4-12) with a normal weight for age but low height for age z-scores. Other mean baseline characteristics of the group \pm SD included BMI (kg/m^2) - 16.7 ± 3.2 ; Total body fat - 20.4 ± 8.3 ; CD4 count 457 ± 397 ; CD4% 19.8 ± 12.4 ; Log HIV RNA 4.12 copies/ml ± 0.74 .

Although only one of these children had been associated with a prior lipodystrophy concern, the study identified eight children (29%) as having fat redistribution which met our criteria for lipodystrophy. Three children had only fat loss and half the children had weight gain only.

Baseline characteristics		
	LD+	LD-
Age, yrs	8.2±2.5	7.2±2.2
BMI, kg/m ²	15.8±2.2	17.1±3.5
Body fat %	19.3±4.8	21.0±9.4
Trunk fat, kg	1.6±1.1	2.3±3.1
Extremity fat, kg	2.44±9.54	2.79±2.33
Trunk/extremity	0.61±.30	0.69±.28
Log viral load	4.77±0.44	3.79±0.64 †
CD4 count (#/dl)	193±198	568±411 ‡
CD4 %	10.1±8.5	23.9±9.4 †

‡P<0.05 †P<0.01

Fig 1. Baseline values in LD+ and LD- children

Changes in weight and body composition in children with and without LD		
	LD+	LD-
Number (%)	8 (29)	20 (71)
Wt, kg	2.9±2.4	3.9±2.3
Total fat, g	-151±324	981±1041 ††
Body fat, %	-2.7± 2.2	0.4 ±4.7 ††
Trunk fat, g	174±296	410±475
Extremity fat, g	-249±213	556±553 ††

††P<0.01

Fig 2. Changes in weight and body composition

Follow-up viral load, CD4 count, and CD4%		
	LD+	LD-
Log viral load	4.20±0.84	3.43±0.74 †
CD4 count(#/dl)	332±248	657±457
CD4 %	14.7±7.8	24.7±11.7 †

†† p=0.06-0.07

Fig 3. Studies with early treatment

Changes in weight and body composition baseline characteristics in children with and without lipodystrophy are shown in figures 1 and 2.

The only baseline factors for these two groups that were significantly determinant were baseline viral load, CD4 count (p<0.05) and CD4% (p<0.01). Age, sex, race, BMI, body fat and trunk extremity ratios were not found to be significant. PI-use (mainly saquinavir and ritonavir) and d4T-use were also found to correlate although no allowance was made for previous NRTI use and the lipodystrophy group were generally more heavily treated. Baseline triglyceride and cholesterol were not significant at follow up, but in the fat redistribution group, in the paired analysis, these did become apparent. Factors associated with >130mg TG were lipodystrophy (OR 11.4, 95%CI 1.0-13.5, p=0.058) and PI use (OR 3.0, 95%CI 1.7-5.3, p=0.02).

In summary, I think our data suggests that body fat changes are occurring in children with HIV; in many cases it is unnoticed or subclinical. In only one of the youngsters included here was there any prior concern about a change in body fat.

We also found an association between lipodystrophy and low CD4 count and CD4 percentage and high virus at baseline. It also seems to be associated with exposure to protease inhibitors and d4T. We found mild increases in triglycerides in children with lipodystrophy and these changes were associated with PI use. We did not find statistically significant changes in cholesterol.

The features of lipodystrophy and the factors associated with lipodystrophy and altered triglycerides in children appear to be similar to those reported in adults but are less severe. Nonetheless, in some of these children the levels of lipid alterations warrant clinical interventions.

It is also important that we concern ourselves with the possibilities that something related to HIV infection and/or its therapies may be putting our paediatric patients at greater risk for later coronary artery disease. At present the estimated increase in risk for coronary artery disease in adults with HIV infection is approximately 0.14% per year. We really need to weigh that against the benefits of decreased mortality that we see with therapy.

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Helping children take HAART:

adherence, taste and formulations

Jeanette Meadway

The Mildmay Hospital offers very intensive support to families with HIV. They have a great deal of experience, not only in helping them take their medicines but also in helping them stay together.

In 1998, the Mildmay Hospital (originally opened for people with cholera at the turn of the century) became Europe's first HIV/AIDS palliative care unit. Since 1993 it has had a family care centre including a children's nursery.

The family care centre has two wards that can accommodate six families. We often have a mother with up to four children in any one of the rooms. Either the mother or the child can be the patient with HIV, and occasionally, a child who is HIV+ can come in with a carer. It is more common for us to have HIV positive mothers with their children, irrespective of whether the children are HIV-positive or not.

One measure of the effectiveness of combination therapy, is that we have had something of a 'baby boom' in the UK amongst HIV-positive women. Our clinic has a particular role to play, allowing the mum to be not only with the new baby, but also with her other children just a few days after delivery.

Sometimes our mothers are IVDUs or on methadone programmes. Often, if the mum and baby were not with us, they would be separated with the baby in special care and the mother going home. Mothers also have to think about taking their own anti-HIV therapy, on top of dealing with the baby's medication. This may be very new to them if they were only diagnosed in pregnancy.

When giving combination therapy to children in the nursery, it is very important that the kids feel happy and secure where they are. I know this sounds like a little thing, but it is not always easy to achieve. Children who are HIV-positive are not always readily accepted in other nurseries.

We arrange meal times with other kids to encourage children to eat. Children who usually never eat anything, can suddenly begin eating very happily in this setting. Seeing other children take their medicine is also helpful.

Staff at the Mildmay are familiar with the medicines and the importance of the regular dosing. This is something that is not true in a generic nursery. It is important to know in detail the individual drug requirements, what they are for, and how important it is to have regular doses. Another benefit is that mothers who have to give kids medication can talk to other mums about how to do this.

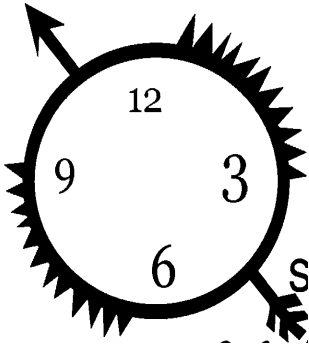
In terms of getting babies to take the meds we tend to always squirt it in orally using a syringe and we teach mothers how to do it at the centre. There are various techniques and afterwards the kid will usually suck on a dummy and take it in without much of a problem. Both AZT and d4T are not too bad in taste but I'm not talking about giving ritonavir. With ritonavir we do tell all mums *'NOT TO MIX IT WITH A FEED IN A BOTTLE'*. I put that in capitals for people who advise mums on how to give medicines. It really does need a large amount of dilution - so it is likely the child won't complete the whole dose if they don't completely finish their bottle - and then you've no idea how much they have had.

Babies quickly get used to taking medication. If children have medication from when they are tiny then it doesn't seem to be any problem in getting them to swallow it - they take it for granted that they have their medicine. All the kids we have had in Mildmay who have taken medication for a long time are in a routine and so it is no hassle. Starting older children can be much more difficult.

Taste and formulations

Here is a brief overview of general opinions of drug formulations we have used at the Mildmay over the last year. This isn't meant to be technical or comprehensive (see the Appendix III on page 37 for more detailed information) but most real responses don't get included in clinical trials.

Taste is particularly difficult to report - especially as children's taste is different to adults. Some drugs with less information reflect the fact that we haven't used them so much.



AZT

The kids like this. (One of our nurses asked me to pass on the information that kids actually love AZT). It is a clear liquid. Newborns have it in syringe and some of them are uncertain about swallowing a syringe full of stuff, but if you put the dummy in afterwards they suck away at it.

We find different centres sending children to us have different regimens and some take it twice a day and some four times a day.

d4T

Children don't mind the taste of d4T but it is not quite as easy to take as AZT. Once it is made up it will last a month and it is not too difficult to store. Some children have this instead of AZT. If the mother is likely to be resistant to AZT, then children are routinely being given d4T instead for the first month after birth. They usually have one month however and then go onto septrin until it is certain that they are HIV-negative.

ddl

ddl comes as a pink cloudy liquid. We describe this to the kids as being like a milkshake and hope that they are convinced! It is given once or twice daily and kids don't tend to mind the taste.

In theory it should be taken on an empty stomach, but this can be a big challenge - have you ever tried to get a tiny baby between feeds to have medicine and then not cry for the next feed? You may have to compromise and do the best you can - and there has been one report that in children the food interaction is less important.

3TC

3TC comes also in a cloudy liquid. We find that the kids don't mind that one too much.

abacavir

Abacavir is now a liquid and you can also crush tablets. You've probably heard that there are some very severe warnings about abacavir for adults and hypersensitivity. Unfortunately some of the symptoms can imitate the ordinary everyday illnesses of childhood.



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nelfinavir

Nelfinavir comes as granules, which you are supposed to make up as a liquid. On the whole we find that nobody takes it. None of our children like it at all and we find that they are happier with tablets crushed to a fine powder with a pestle and mortar.

Most of our mums come into us with the granules and after about a day and a half we phone up their treatment centre to get the tablets instead. Nelfinavir does not taste too bad but it is an absolutely lurid blue and it is difficult to disguise the colour in anything.

ritonavir

Ritonavir really is foul and children are often able to get it in through a gastrostomy-tube. I would not like to have to give my child ritonavir.

Fatty foods disguise the taste a little, but sweet ones don't seem to at all - so sugary things don't seem to have the slightest effect. Some people think peanut butter or chocolate may help.

Some kids will start co-operating by having it in a syringe and putting it themselves into their mouth and I think that is the only hope for bigger children. But for the very small ones who don't understand why they are having medicine I would not fancy trying to give ritonavir liquid.

nevirapine

Nevirapine comes as a cloudy suspension. The tablets can also be crushed as well and we have found that either of these are acceptable to most of the kids. Obviously there is a risk of rash with nevirapine.

efavirenz

Efavirenz is only recommended for children older than three years. I have problems with our adults starting efavirenz in that they have really ghastly dreams and some have extreme agitation, but this has been less of a problem with children, although it may be that children experience these symptoms but cannot describe them.

Dr Jeannette Meadway is Medical Director of Mildmay Hospital in London, the leading UK specialist HIV palliative care unit, caring for men, women and children with HIV. She is the consultant for the family care unit, including a children's nursery and inpatient unit for mothers with their children. A specialist in HIV medicine and internal medicine, until 1997 she was lead clinician in infection and immunity at Newham General Hospital in East London.

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Community Support in France

Alain Volny-Anne

Sol en Si is a community organisation in France founded to support and help families and children with HIV.

Sol en Si is a French organisation that specifically works with families with HIV. It was created in 1990, before the emergence of antiretroviral therapy and the current success in preventing mother-to-child transmission. The ACTG 076 results only came out in 1994, so we can consider 1990 as the peak of the epidemic (at least in France). When we were established, existing organisations were considered either as gay or drug-user orientated. Therefore, we felt that specific support for families with HIV was needed.

Services for children

The organisation is structured so there is always a day nursery for the very young children, which is open from 8am-8pm. This means that working parents can bring their kids, or if someone just needs a rest they can bring their kids just for the day. We also have a transport system to take kids to hospital for examinations and consultations.

One of the first services we provided was volunteers – buddies, to accompany the families, either for the children alone or for the parents as well, depending on what they required. In 1990 people with HIV often had short life spans and helping someone with HIV could be very difficult for the volunteers. Nowadays things have changed and volunteers will often work with families over a long period so it's a totally different situation, but a happy one. We also provide a holiday service - every year a certain number of kids go on holidays with volunteer families, sometimes for one or two months.

We also have what we call emergency foster care in case a mother is very ill and is taken into hospital (this is used less and less now fortunately, due to the current therapeutic background). Then we have volunteers come and pick up the children and keep them at home as long as necessary. This volunteer would then take the child to see his parents in hospital (everything is organised around this) and take them to school.

My own work is in the health workshops in the Paris sites. Twice a week I have one morning dedicated to health workshops so parents can come to me and ask me for information on treatments and about their own health and their children's. Here we address many treatment issues including adherence.

Sites

Our first site opened in Paris in 1991. Now we have two in Paris, two in the Parisian suburbs where lots of immigrants live, one in Marseilles, one in Nice, two cities in the south that have a lot of IV drug users, and French Guyana which is in South America but a French department and also a very specific site

because in French Guyana there is a lot of immigration from Surinam, Brazil, Haiti and Guyana. In French Guyana, the rate of infection is one of the highest in France after Paris and in the south of France.

Clients

As we got more and more busy with our first site there was increasing demand due to word of mouth, particularly in the African communities, most of our families are immigrants, about 80% and 20% are IV drug users or ex IV drug users. About 98% our our clients would be classed as being in some way socially disadvantaged.

Today and the future

Today the situation has changed a lot. Fortunately fewer and fewer children are born with HIV in France, but even so we see more and more arriving from Africa who are then diagnosed in hospitals and then referred to us.

We are now wondering if we should open the services to children with hepatitis C, not co-infection only, but also with hepatitis C only. And should we close down some of the nurseries? - maybe they are not as necessary as they were before. The problem is that most of the families that are used to us are not very happy about the idea of sending their kids to city day nurseries, probably for reasons of confidentiality, even though by law it is forbidden in the city nurseries to disclose someone's status. We also surveyed some of those city day nurseries and most of the staff told us they were not ready to welcome HIV-positive kids - so we have to deal with this. Adolescence is a really big issue for us now - we haven't yet decided on how to best serve this growing population.

By the end of 1999 we had received 271 new families, which represents 489 kids. When 1074 families have called on us for any reason in the same year we all remain convinced of our reason for being. This conviction I hope will help us through these new decisions.

What I regret concerning the adherence issue though is that although I have requested many times that the social department of the ANRS (which is our national research agency) evaluate how adherence is improved with the support of all our services, it has not yet been done officially. But I believe that supporting the family in the community is a factor in good adherence for these children.

Alain Volny-Anne is currently working at Sol en Si, an organisation providing services to families with HIV in France. He is a treatment activist and a member of the European AIDS Treatment Group (EATG) and the European Community Advisory Board (ECAB) and represents these organisations on the PENTA steering committee. volny-annealain@voila.fr

Simplifying adherence: the approach to using g-tubes in the US

Lisa Frenkel and Octavio Ramilo

Gastrostomy tubes (g-tubes) can really assist some kids and families with adherence. However they do not always increase adherence when a family is not disciplined enough to give the medicine or if, even more often, they really don't believe in the medicine, they're not sure about the medicine or they are worried about the medicine's toxicity. In this case putting a gastrostomy tube in is not the answer.

They are actually placed very easily - with endoscopy or during surgery - and we haven't seen any serious complications. However minor complications do occur; the tubes get plugged so you cannot put nelfinavir powder in (or at least we haven't figured out a way).

The g-tube can occasionally fall out, but some of the parents now know how to put them back in! Stomach fluid can leak out of the hole, which can worry people. This is solved by putting

in a smaller tube in for while until the hole shrinks down and the larger tube can then be put in again.

A complication which occurs more frequently is that you can get granulation tissue (which can also bother the family because of its appearance). If this occurs you just use silver nitrate to burn it off chemically.

Regardless of the insertion method, the first tube placed usually has a three to four centimetre appliance inside the stomach, no valve and approximately ten centimetres of tubing protruding from the abdominal wall - called PEG or Malecot in the US. Once a track is formed - this takes about six weeks - a smaller 'button' type of tube with a one-way valve (Bard or Mic-Key) can be placed. Most families can reinsert the small g-tube at home if it comes out and if it dislodges in the stomach it will pass through the intestines without complication.

GASTROSTOMY-TUBES: A USEFUL TOOL IN PAEDIATRIC HIV CARE

A few years ago, gastrostomy tubes (g-tubes) were introduced in our clinic to help provide nutritional support for some of our children. As a result, our hospital now has a group of paediatric surgeons and gastroenterologists with significant experience in placement of these devices who are very committed to this. When we began using HAART more routinely, we noticed the difficulties associated with the giving a triple or quadruple antiretroviral regimen to some of the children, and we realised that a g-tube could be a practical solution to improve both tolerability and adherence.

Currently, we have 10 children (aged from 17 months to 12 years) who have g-tubes exclusively for making adherence easier. The individual circumstances and situations vary in each case, but overall the experience has been very positive. We have had few and only minor complications (occasionally a leak or local irritation). In the past few years, among infants who started triple therapy in the first 2 months of life, we noticed that it is relatively easy to give the medication during the first year. The second year becomes quite challenging though and a few children have benefited from g-tubes.

Under the right circumstances, g-tubes provide significant advantages. Clinically, with improved tolerability and compliance, we have observed better viral load reductions, and improvements in CD4 counts and overall general health. In addition, by making it less stressful to give medication, without needing a struggle, some of the mothers have been able to interact with their children in a more positive way. This has provided them with a more rewarding experience in the context of their already complicated lives.

Obviously, despite the limitations of our experience and the small number of children included, we believe that children can benefit from this approach and that it should be considered as an additional useful aid in paediatric care.

'I prefer using my g-tube to swallowing pills even though I can taste the ritonavir a bit.'

Child with tube

'I couldn't fight with my daughter any more because I thought that she would hate me. So before the gastrostomy tube I just didn't give her the medicines.'

Mother

'Now we have the gastrostomy tube we don't have to fight with our son because we can give him the medicines when he's asleep.'

It is a lot easier to give the medicines on schedule.'

Mother

*'For children I've become more and more convinced with using g-tubes. It can be a psychological barrier for some doctors, but it is much less invasive than a central line which has more complications and which are used routinely...if my own child needed to take this many pills, I would **insist** on a g-tube.'*

Dr Grace Aldrovandi

Reducing paediatric infections: *antiretroviral use in*

Karen Beckerman

The program at San Francisco General Hospital for perinatal care focuses strongly on maternal health. This strategy has reduced their incidence of vertical transmission to practically zero, and they believe that ‘nothing is more important to a child than the health of its mother.’

Something that other speakers have raised and which I would like to additionally stress - is that pharmacokinetics of antiretrovirals in children is extremely important. Many other aspects of HIV care are also important for babies and children, however nothing is more important to the health of a child than the health of its mother. It is from this perspective, with a very strong focus on maternal health, that our programme in San Francisco, at the Bay Area Peri-natal AIDS Centre has grown up since it was founded in 1989.

We have benefited in many ways from being in San Francisco. We have the support of the HIV community, access to the cutting edge of HIV therapy, and access to the tremendous HIV advocacy that has been a long-standing tradition there. Compared to the other presentations we are somewhat behind in terms of support for families.

For example, I just had to take care of three women in the last year, all of whom had HIV-uninfected babies but none of whom were able to take their babies home with them. And they will probably never live with their babies in their entire lives. This kind of tragedy cannot be averted by all of our pharmacological interventions, but it can be helped with very important programmes like the ones we have just heard about.

It is important to remember the first results from what I now call an ‘historic relic’ - ie the 076 study. At the time it was a miracle - the first sign of true hope in an otherwise very bleak picture. But now we have moved far past that in terms of HIV therapy and the idea now of giving monotherapy to anybody except to pregnant women or uninfected babies is really an anathema. And it should become an anathema to pregnant women also. The treatment protocols that I will be discussing are controversial, but I want to make it very clear that pregnant women deserve no less than the absolute latest standard of care and optimal therapies.

We knew from the 076 study that we could cut the rate of vertical transmission using AZT by itself prophylactically for both mum and baby. What we also knew by the mid 1990s was that viral load was highly predictive of progression to AIDS. What we then hoped (although none of us really knew it yet) was that if we could reduce viral load we could perhaps lower a person’s risk of progression to AIDS or to death.

In the case of our unit, where we were taking care of pregnant women, we did not know if lowering a mother’s viral load by use of these potent combinations could also perhaps benefit the baby? Many people were thinking of HAART therapy as a threat to neonatal immunal health, but we saw it as a chance to benefit the babies health. I would stress to you some of the reasoning behind this because we were really in an unknown area. However as obstreticians, we did know that the baby is

exposed to enormous amounts of mothers blood during pregnancy. In the third trimester alone a foetus is exposed to 80,000 litres of maternal blood. In the case of an HIV infected mom that means 80,000 litres of virus. So we reasoned that it couldn’t help but be of enormous protective benefit to the foetus to aggressively lower plasma viremia during gestation in the second half and later in pregnancy.

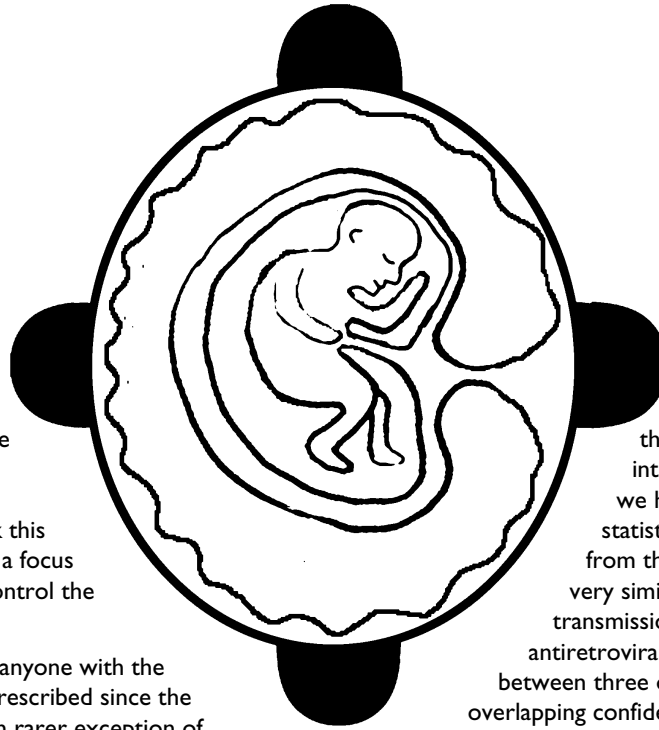
Of course we had concerns about the developing foetus and we were all very nervous about what might happen in terms of birth defects. Our first mothers using HAART therapy and PIs, were women who otherwise would have been dead without that therapy, they all had advanced HIV disease, AIDS and a history of PCP. So, there was not really much of an option in discontinuing their HIV treatment. We have since given the mothers the option to discontinue therapy before or during pregnancy, although none have chosen to do this yet.

We also developed an attitude towards the care we give our patients which I tried to sum up in a sort of Bill of Rights for HIV-positive mothers. This is for access to current state-of-the-art therapies for both HIV disease and pregnancy. In terms of pregnancy we can’t always reach these goals, but access to pre-diagnosis discussion with the mum about what she wants for herself and her foetus. It should include Lamas classes (pre-natal) orientated towards HIV where they don’t have to sit hour after hour learning about the beauty of breast-feeding! Also (and this is very important to the women that I take care of) knowing that when they are admitted San Francisco hospital, the body fluid protections that will be taken by their carers are identical to those that every patient receives. In other words every patient in our hospital is treated as if she could have a fluid borne pathogen that could affect contacts - HIV mums are treated no differently to any other mother. This is a great comfort to everyone.

Education and counselling is the centrepiece of our work. It is what we spend most of our time on in our very long and frequent discussions. Mothers then know that they are in charge and they will determine what therapies they will take during pregnancy (and what therapies they don’t take). Empowerment is a very important part of our orientation. This may seem altruistic of us, but it is actually quite practical - there is no way that you can force anyone to take therapy that she doesn’t want to. All your going to do is to force her to tell you that she is doing what you want her to do.

We find that when mothers know this, they are very honest in telling us about their adherence, about how many meds they really did miss that week. This can explain a viral load that is inexplicably high and it really is an enormous boon to our relationship with individual and collective patients.

pregnancy



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But our treatment guidelines have evolved since the 076. When in 1994 AZT was available to all mothers, our clients quickly took this up, but by 1996/97 we shifted to a focus of the use of antiretrovirals to control the mother's viral load.

We no longer give two drugs to anyone with the rare exception of d4T/ddI (not prescribed since the recent FDA caution), and an even rarer exception of AZT being given to mothers in early stage disease, when mothers feel that they are just completely unable to consider triple therapy.

The standard of care for HIV-positive people is now a minimum of triple therapy, and it is our philosophy that it should be the standard of care for pregnant women. With early disease, mothers can always stop their medicines after they deliver. But it is our charge to safeguard the mothers' health, to enhance their survival, and our duty to make sure the babies that we care for are delivered uninfected of a mother who is not in the process of developing completely unnecessary antiretroviral resistance. Recently we've had three mothers deliver on more than four drugs.

So can you really control maternal viral burden in pregnancy? You can, but you can't do it with no drugs or just one. Two drugs can be effective but we all know from other adult studies that the development of resistance is extremely likely - and this will then compromise the mother future options. Data has appeared in pregnancy showing that about 80% of women who receive AZT alone will develop broad-spectrum nucleoside resistance.

Not surprisingly, the benefits from triple therapy is completely predictable from what is well known in adult and child studies. We are benefiting mother's health tremendously by treating her disease accurately with a minimum of three drugs

We have been talking a lot about mum's health, but what about the effect upon baby of all these meds? For example there were early concerns about prematurity with PI use. Even with our own data the relatively low numbers that we see mean that the results do not achieve statistical significance. However, there is no documented increase in prematurity going from zero to three or more antiretrovirals. In fact our babies who were most likely to be premature were born to those mothers who received no drugs during pregnancy, and we see no decline in gestational age in comparison to antiretroviral use.

With transmission rates too, our small numbers of transmissions mean they are lacking in statistical significance. I

therefore reviewed the available international literature, to see if what we had witnessed in San Francisco was statistically true. Combined reports from thirteen different studies saw data very similar to ours with falling transmission rates as number of antiretrovirals are increased. The difference between three or more, or two drugs, still has overlapping confidence intervals, but I expect that as we gather more numbers internationally that we will see that the best thing for baby is three or more drugs.

The issue of ruptured membranes, very beautifully studied by Landesman and colleagues in the WITS protocol, demonstrated that with increase in hours of ruptured membranes there is an increase in probability of transmission. This concern has of course led to the common practice in many areas of elected caesarean section to prevent HIV-transmission. Our data from San Francisco was gathered in a population where elected caesarean section was available only for the last ten deliveries. The uptake in these cases has been around 25%. We do not withhold caesarean section for those mothers who want it, but for those mothers with good virological control we advise them that there is no demonstrated benefit for them or their baby from an elected surgical intervention.

And finally I must address why the most popular therapy for pregnant women in America is still Combivir alone. I still attend professional obstetrical meetings where leaders in the field (though not experienced in HIV), talk about the beauties of Combivir and how ideal it is for pregnant women.

I answer that just because you hear it and from someone who appears to be in a position of authority it doesn't mean it is true - in fact it is very wrong. A woman who receives Combivir alone in pregnancy regardless of her stage of disease, has a four out of five chance of becoming resistant to all nucleosides for the rest of her life.

This is not a tolerable action. Many of us would call it not only outside of the standard of care but malpractice.

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Treatment for newly born babies

Di Gibb

The US guidelines for infected infants recommend initiating therapy for all babies diagnosed under twelve months old. The rationale is similar to treating primary infection in adults - but treating babies this young is complicated and not always very successful.

I thought I would just start by showing the estimated drop in the vertical transmission rate that we have seen in the UK shown in Figure 1, which was published in the *BMJ* at the end of 1999. We have tended to have more elected caesareans here compared to the US and perhaps less triple therapy. However certainly through 1999/2000 many more women were going onto triple therapy at least for the duration of pregnancy.

I am not going to say a lot about follow up of babies born to positive mothers who are not infected, or how you manage indeterminant babies. There are of course issues that have been raised, especially in France about mitochondrial toxicity, which has raised the need for longer-term follow-up, especially as more women are taking more drugs.

Using PCR tests we are now able to make an early diagnosis of whether a child is infected with HIV. In the first day or two of life only about 40% of babies will be PCR positive on these techniques, but as the sensitivity rises rapidly, they can virtually all be diagnosed by three months. We haven't completely sorted out how the use of potent antiretroviral therapy that might happen affects the accuracy of diagnosis.

There have been a lot of discussions recently about when to start treatment, and in adults there is a move to saying we should be starting later, maybe not until CD4 count approaches 200 cells/mm³. In children the issues are more difficult because we don't have such good surrogate markers in kids. Should we start in primary infection soon after birth? If all mothers knew about their HIV status in pregnancy, then we would have fewer babies who were HIV-infected, and we would certainly know about most of them. Should we base the decision on HIV viral load or CD4 count or perhaps their rate of change with age? Using the PENTA, the PACTG, and data from a number of cohorts we are trying to look at how quickly CD4 and viral load these have changed in untreated children with increasing age.

The US paediatric guidelines for starting antiretrovirals have suggested that therapy should be initiated in all infected infants if they are diagnosed less than twelve months of age. To some extent that has been followed in Europe, although with quite a lot of caveats. I think it is definitely not evidence-based but there is an enormous feeling that we have to do something when a baby is found to be HIV-positive, especially if the mother was taking ART. It is always a pretty devastating situation.

Rationale for early treatment is equivalent to primary infection



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in adults, as we know within a fairly tight window when babies were infected. Also, from historical data we have evidence that about 20% of children have rapid disease progression and risk progression to AIDS or death in their first year of life. Control of HIV viral load, allowing normal development of the immune system in infants may also be very important because they acquire this virus when they are immunologically immature.

Children have different immune systems from adults; they have a very active functioning thymus, which may be good. They have higher levels and more variation of CD4 cells, which only really decline to adult levels by the age of five or six years. This means that we have more difficulty in predicting what is going to happen to those kids according to their CD4 count alone.

For example, children can have PCP with CD4 counts of 1400-1500 cells/mm³ (which is unheard of in adults). When you put children on HAART, you mostly see an increase in CD4 naive cells, and this again is a different pattern from the response in adults, it shows a more active thymus. They also have a different pattern of RNA decline, by over a log over the time from birth (a rise after birth and then a slow fall to 5 years). Certainly there is a relationship between viral load in babies under one year and risk of progression but the positive predictive value is not good. You can say that a child with a low viral load will do okay but a child with a high viral load may not or may do well. This is not very helpful and is an area in which we need more information.

Figure 2 lists antiretrovirals available at the end of 2000 and highlights the inadequacy of PK data in infants. We have rather a dearth of data for under two year olds for any of the PIs. Ritonavir has been most used in infants, but one of the problems with PK studies is that we have only small numbers eg 10, 12, 20 children across all the age ranges. This means only a few results are relevant for children under two. Getting PK in children under two is very difficult, but is also very important for the PIs and probably the NNRTIs as well.

In Katherine Luzuriaga's PACTG356 study, 15 out of 24 babies under three months of age who started on treatment saw their viral load fall to <50 copies and remain there to 2 years. She then studied these fifteen babies with two babies from a previous study who also had undetectable viral loads. Regimens used included: five children on triple with nevirapine, five on four drugs with nevirapine and abacavir and seven children on four drugs with nevirapine and nelfinavir. Sixteen out of

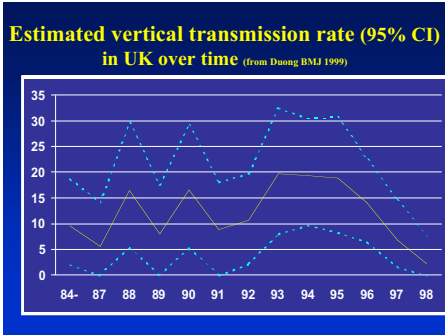


Figure 1. Vertical transmission rates in UK

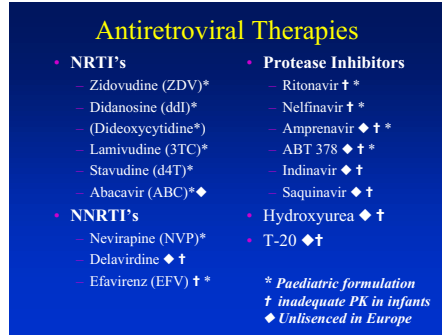


Fig 2. ARV therapies available in Oct 2000

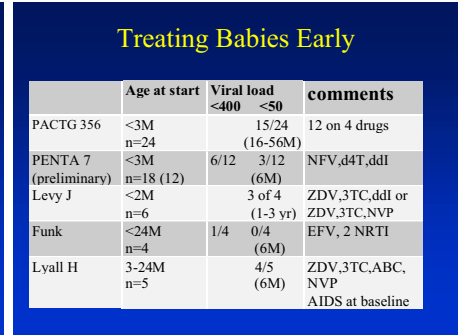


Figure 3. Studies with early treatment

seventeen became seronegative by sixteen months and HIV-I specific lymphoproliferative responses were not detected, although proliferative responses against other antigens were. This may be worrying, because one would hope to preserve those responses against HIV after primary infection, and this is a different situation from that seen in adults where responses are preserved. This has resulted in lots of discussions about the possibility of giving vaccines to try to induce more HIV-I responses after viral load has been suppressed to below 50 copies/mL in babies.

We have also done a similar study in Europe - the PENTA 7 study, where we looked at the toxicity, tolerability and activity of early therapy with d4T, ddI and nelfinavir. We also looked at the pharmacokinetics of nelfinavir in very young babies. We started with quite a high dose of nelfinavir - 120 mg/kg/day - which we increased to 150 mg/kg/day when the results from the first four babies showed low trough levels on 120 mg/kg/day (Note that this is five times the equivalent dose that you would give to an adult).

The data are fairly preliminary but the first thing we found was that nelfinavir powder was poorly tolerated and crushing up the tablets was much better. However even increasing the dose to an average of 150 mg/kg/day, we still observed inadequate trough levels. Also we have had quite disappointing results of activity. Of the twelve children out to week 24, only 50% have seen their viral load reduce to below detection to less than 400 copies/mL and only a quarter are below 50 copies/mL.

It is worrying that we were not more successful, especially given the data presented earlier (see Figure 3, and pages 12-13). Giving four drugs to five babies who were all quite sick with much lower CD4 count seems to produce a much better response, with four out of five of them achieving viral load levels below 50 copies/mL. Of course you don't want to wait until a baby gets an opportunistic infection with PCP or CMV before you start giving treatment, as it can happen very quickly with some babies. However it may be that adherence is much better in babies that have had symptoms.

What about clearing infection? That is one reason why people started treating primary infection both in adults and in children. The theory is that if you stop treatment after starting early, you could reset the viral set point? These are the reasons for thinking about starting, but what about the disadvantages? Some children may not need treatment for many years, and there are concerns about toxicity, poor tolerability, adherence and whether you are getting the right dose. It is easier to be surer

that you are going to get the right dose when the child is a bit older, particularly for PIs and possibility NNRTIs.

Regimens need to be chosen based on tolerability, PK and support for adherence - and this is vital. Management for toxicity means planning for what happens if side effects become apparent and what do you do if the management of side effects is unsuccessful? You need to plan ahead. If you succeed virologically, how long are you going to keep children on the same treatment? Forever? If you decide to defer treatment and monitor, is your decision to start based on a rate of change in CD4 a percentage as well as absolute values?

These questions need to be addressed but we only have results from smaller studies and no randomised studies. With such small numbers, we all need to work together to pool our data.

If a child is just not responding and you decide to switch to another regime or even to stop - then having a blood sample before stopping for HIV resistance testing at the time could be important. Resistance in children is a critical issue that we need to become acutely aware of especially if you start with all 3 classes, which I'm not in favour of. The data from the Palella study in adults attending US clinics showed the average time on HAART regimens to be only twelve months for the first, eight months for the second, seven months for the third treatment regimen. By the time you got to your third regimen you are usually on four or five drugs after being on three or four for your first.

Mike Sharland reported similar sorts of data for children in Durban. Hopefully some of our children are going to live for twenty or thirty years and they could run out of all classes of drugs in two years. We know from these data that you are half as likely to respond to your second regimen as your first regimen.

Dr Diana Gibb currently works on paediatric trials at the newly formed MRC Clinical Trials Unit (CTU) in London, and also does clinical work at Great Ormond Street Children's Hospital, where she set up the paediatric HIV service. She was instrumental in setting up the PENTA network. She established the first family HIV clinic in the UK at GOS and a similar clinic at Newham General Hospital in East London. She is author to many publications on HIV-infection in children and has lectured widely nationally and internationally on paediatric HIV infection.
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Appendix I: Pill swallowing protocol

Family HIV Service, St. Mary's NHS Trust.

The worker who will be carrying out the instructions with the child should be a neutral member of the team who has no prior history with the child. Ask parents not to let the child drink before coming to the clinic so they are slightly thirsty, as s/he will have to drink water during the session.

Obtaining information

At the appointment, meet with the parents alone initially, in order to explain the procedure and gather information. The following questions are important:

- How well does your child eat?
- Does your child have a good appetite and eat a variety of foods?
- Are meal times difficult, stressful or overly long?
- Can your child swallow meat or other chewy foods?
- Has your child ever had to take pills before?
- Could s/he manage them?
- Has your child ever choked on pills or had any difficulties swallowing them?
- How does your child manage liquid medication?
- How is your child managing at school? (This may highlight difficulties following instructions or learning in general).
- Does your child have lactose intolerance? (Placebos contain lactose).
- What have you told your child (if anything) about taking pills?
- Is there anything else we need to know about your child?

Setting the scene

Parents should be out of the room for the session. To avoid possible disruption later, the child should be encouraged to use the bathroom beforehand. The room used must be free from distractions such as toys or books. A sign on the clinic door will help prevent interruptions.

The worker and child should sit across from each other at a small table. Talk enthusiastically about what the child will learn during the session. This will help establish a rapport. It is important not to hold up the process by chatting about other things. Explain to the child that s/he will be learning how to swallow pills.

It is helpful to mention that the good thing about pills is that you don't taste them when you swallow them and that pill taking will be much quicker than taking liquids. It is important not to let the child know that they will soon be taking a new kind of pill as this may deter them from learning the technique.

The Process

Before the first attempt, encourage the child to swallow a mouthful of water. This may help demonstrate any problems the child has with swallowing and the general level of motivation.

Demonstrate the steps to pill swallowing as follows:

- Sit or stand up straight
- Take a deep breath
- Breathe out with pursed lips, making an 's' sound.
- Put the pill in the middle of your tongue.
- Keep your head straight.

Keep the range of pill bottles that will be used out of the child's sight. Present the child with the first (smallest) pill, placing two pills

on a piece of paper. Let the child choose which pill they want to swallow. Show the child how to swallow the pill by going through the steps as outlined above. Then encourage the child to swallow the pill themselves, reminding them of the steps. You can hold the child's chin gently in order to keep their head straight. A mirror may be useful to help show the child where to place the pill.

Maintain a neutral face and tone of voice throughout, but praise the child for his/her effort, in particular after the pill has been swallowed successfully. Social reinforcement is the primary reward for successful pill swallowing. Rewards such as sweets, toys should not be used unless absolutely necessary.

If the child has difficulties swallowing a pill, encourage the child to repeat the process with another pill of the same size before moving on to the next pill. The child can also teach the worker the correct way to take the pill. Both these moves will help increase their confidence.

If the first or second pill cannot be swallowed on the first attempt, encourage the child to say, 'It's OK, I just need to keep trying'. It is important not to mention this with later pills as this may reinforce the child getting the pill stuck.

When moving from one pill to the next, it is important **not** to mention that the child is moving on to taking a *bigger* pill but the *next* pill. Any mention of size may increase a child's anxiety. Direct the child to swallow the next pill without asking them if they can do it. Repeat the process as before by using short, repetitive commands, reminding the child of the steps and maintaining a neutral expression throughout.

Repeat the process until the largest pill the child can manage has been swallowed. As the session progresses, decrease the amount of coaching and instruction but continue to praise the child when successful. The worker is more involved when the child is successful than when s/he is unable to complete the task. This will encourage the child to continue.

Limit the session to half an hour – any longer and the child will become tired and frustrated. End the session on a positive note. When the child has demonstrated the technique successfully, ignore them while they are swallowing, only paying attention and praising when they have completed the task. When the child has demonstrated that they can swallow pills successfully, it is no longer necessary to coach them.

And finally...

At the end of the session, bring the parents into the room so that the child can show off their new skill. Instruct the parents to sit to one side quietly, withholding comments or praise until the child swallows successfully.

If parents are supportive and keen to be involved, send them home with enough pills of the largest size the child is able to swallow so that they can practice once a day for a week (until the next appointment). Parents should be supplied with written instructions so that they can practice with the child. Parents are advised to stop practising if the child experiences any problems during the practice at home so that negative experiences are kept to a minimum. Contact details should also be given to parents so that they can ring the clinic if they have any problems or have any questions.

Appendix II: Antiretrovirals used in paediatric treatment

This summary of drug formulations, doses and food interactions has been adapted from the Appendix I of the US Guidelines for Treatment of HIV-infected Adolescents and Adults (Jan 2000). Updated information has been provided by the pharmacy department at Gt Ormond St Hospital for Children and each drug manufacturer. Paediatric dosing is often based on limited data and is liable to change as new information becomes available. Usage in clinical practice can often differ from doses recommended in licensed SPC.

The full US documents include important information on the side-effects, PK pathway and drug interactions for each drug. The US Paediatric HIV guidelines are available from the internet on the same site at <http://www.hivatis.org>

Drug name	Preparations:	Dosage:	Special instructions:
Abacavir (ABC) Ziagen™	Paediatric oral solution: 20 mg/mL; Tablets: 300 mg In UK abacavir is used off-label for children under 12 years	Neonatal dose: Not approved for infants less than 3 months of age. In infants between 1 and 3 months of age, a dose of 8 mg/kg of body weight twice daily is under study. Paediatric/adolescent dose: 8 mg/kg of body weight twice daily, maximum dose 300 mg twice daily. Adult dose: 300 mg twice daily.	Can be given without regard to food. Patients and parents must be cautioned about the risk of serious hypersensitivity reaction. A medication guide and warning card should be provided. Patients in the US experiencing a hypersensitivity reaction should be reported to the Abacavir Hypersensitivity Registry (1-800-270-0425).
Didanosine (dideoxyinosine) (ddI), Videx®	Paediatric powder for oral solution: 2g, 4g bottle for reconstitution with antacid, named patient only; Chewable tablets with buffers: 25, 100 and 150mg; 'Reduced mass' with buffer: 200mg; Enteric coated formulation 125, 200, 250, 400mg	Neonatal dose (infants aged <90 days): 200-240 mg per m ² of body surface area every 12 hours. * US guidelines 50mg/m ² every 12 hours. Paediatric dose: In combination with other antiretrovirals, 200-240 mg/m ² of body surface area per day taken either once or twice daily. (Note: may need higher dose in patients with central nervous system disease.) Adolescents/Adult dose: Body weight >60kg: 400mg per day, either once or twice daily. Body weight <60kg: 250mg per day, either once or twice daily.	<i>For formulations containing buffering agents or antacids:</i> Food decreases absorption; administer ddI on an empty stomach (at least 30 minutes before and 2 hours after a meal). When administering chewable tablets, at least two tablets should be administered for children over one year of age to ensure adequate buffering capacity (e.g., if the child's dose is 150 mg, administer two 25-mg tablets and one 100mg tablet and not one 150-mg tablet). Children <1 year should receive a single dose. <i>For oral solution:</i> shake well and keep refrigerated; admixture is stable for 30 days. <i>For ddI/EC (without buffer):</i> Food decreases absorption; UK HIV Pharmacist Group recommend not eating for two hours either side of the dose until ongoing studies clarify post-dose interaction. ddI/EC not recommended for children under 6 years old.
Lamivudine (3TC), Epivir®	Solution: 10 mg/mL; Tablets: 150 mg	Neonatal dose (infants aged <30 days): 2 mg per kg of body weight twice daily. Paediatric dose: 4 mg per kg of body weight twice daily. Adolescent/Adult dose (>12 yr): Body weight >50 kg: 150 mg twice daily. Body weight <50 kg: 2 mg per kg of body weight twice daily.	Can be administered with food. For oral solution: store at room temperature. Decrease dosage in patients with impaired renal function.
Stavudine (d4T), Zerit®	Solution: 1 mg/mL; Capsules: 15, 20, 30, and 40 mg.	Neonatal dose: under evaluation in PACTG 332. As paediatric dose. Paediatric dose: 1 mg per kg of body weight every 12 hours (up to weight of 30 kg). Over 30kg as adult. Adolescent/Adult dose: Body weight >60 kg: 40 mg twice daily. Body weight <60 kg: 30 mg twice daily.	Can be administered with food. Need to decrease dose in patients with renal impairment. For oral solution: shake well and keep refrigerated; solution stable for 30 days.
Zidovudine (ZDV, AZT), Retrovir®	Syrup: 10 mg/mL; Capsules: 100 mg; Tablets: 300 mg; Concentrate for injection/for intravenous infusion: 10 mg/mL.	Dose for premature infants: (Standard neonatal dose may be excessive in premature infants.) Under study in PACTG protocol 331: 1.5 mg/kg of body weight every 12 hours from birth to 2 weeks of age; then increase to 2 mg/kg of body weight every 8 hours after 2 weeks of age. Neonatal dose: Oral: 2 mg/kg of body weight every 6 hours. Intravenous: 1.5 mg/kg of body weight every 6 hours. Paediatric usual dose: Oral: 160 mg/m ² of body surface area every 8 hours. Intravenous (intermittent infusion): 120mg/m ² of body surface area every 6 hours. Intravenous (continuous infusion): 20 mg/m ² of body surface area/per hour. Paediatric dosage range: 90 mg/m ² of body surface area to 180 mg/m ² of body surface area every 6-8 hours. Adolescent/Adult dose: 200 mg three times a day or 300 mg twice daily.	Can be administered with food (although the manufacturer recommends administration 30 minutes before or 1 hour after a meal). Decrease dosage in patients with severe renal impairment. Substantial granulocytopenia or anemia may necessitate interruption of therapy until marrow recovery is observed; use of erythropoietin, filgrastim, or reduced ZDV dosage may be necessary in some patients. Reduced dosage may be indicated in patients with substantial hepatic dysfunction. Infuse intravenous loading dose or intermittent infusion dose over 1 hour. For intravenous solution: dilute with 5% dextrose injection solution to concentration <4 mg/mL; refrigerated diluted solution is stable for 24 hours. Some experts in paediatric HIV infection use a dose of 180 mg/m ² of body surface area every 12 hours when using in drug combinations with other antiretroviral compounds, but data on this dosing in children is limited.

Drug name	Preparations:	Dosage:	Special instructions:
Efavirenz (DMP-266) Sustiva™	Capsules: 50, 100 and 200 mg. doses Syrup - 30mg/ml (doses) Syrup available on named-patient programme.	Neonatal dose: Unknown Paediatric dose: Indicated for >3 years old and >13kg only. Administered once daily. Capsules: Syrup: Body weight/mg 13-15 kg: 200 mg; (270mg=9ml) 15 to <20 kg:250 mg; (300mg=10ml) 20 to <25 kg:300mg; (360mg=12ml) 25 to <32.5 kg:350 mg; (450mg=15ml) 32.5 to <40 kg:400 mg; (510mg=17ml) >40 kg:600 mg (600mg=20ml) There is currently no data available on the appropriate dosage for children under age 3 years. Adult/adolescent dose: 600 mg once daily	Efavirenz can be taken with and without food although side-effects may be reduced if taken with food. Relative bioavailability of efavirenz was increased by 50% (range 11-126%) following a high fat meal (1070 kcal, 82 grams fat, 62% of calories from fat - equivalent to 8 Milky Way bars in one sitting). As there is no information on safety of efavirenz when given above the recommended dose, administration with a high fat meal should be avoided. Capsules may be opened and added to liquids or foods but efavirenz has a peppery taste; grape jelly has been used to disguise the taste. Bedtime dosing is recommended, particularly during the first 2-4 weeks of therapy, to improve tolerability of central nervous system side effects.
Nevirapine (NVP) Viramune®	Suspension: 10 mg/mL; Tablets: 200 mg.	Neonatal dose (through age 3 months): Under study in Paediatrics AIDS Clinical Trial Group protocol 365: 5 mg/kg of body weight once daily for 14 days, followed by 120 mg/m ² of body surface area every 12 hours for 14 days, followed by 200 mg/m ² of body surface area every 12 hours. Paediatric dose: 120 to 200 mg/m ² of body surface area every 12 hours. Note: Initiate therapy with 120 mg/m ² of body surface area administered once daily for 14 days. Increase to full dose administered every 12 hours if there are no rash or other untoward effects. <i>Note: Gt Ormond St recommend 4mg/kg once daily for the first 14 days, then 7mg/kg twice daily for children under 8 years old and 4mg/kg twice daily for children over 8.</i> Adolescent/Adult dose: 200 mg every 12 hours. Note: Initiate therapy at half dose for the first 14 days. Increase to full dose if there is no rash or other untoward effects.	Can be administered with food. May be administered concurrently with ddI. NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves. NVP should be discontinued immediately in patients who develop severe rash or a rash accompanied by constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering). Suspension must be shaken well; store at room temperature. <i>NOTE: EMEA requires fortnightly monitoring including liver function test every two weeks for the first 8 weeks.</i>
Amprenavir APV Agenerase	Paediatric oral solution 15mg/mL; Capsules:50 and 150mg.	Neonatal Dose: No pharmacokinetic data on dosing in children less than 4 years old. Paediatric/Adolescent Dose (<50kg): Oral Solution: 22.5 mg/kg bid or 17mg/kg tid (maximum daily dose 2,800 mg). Capsules: 20 mg/kg bid or 15 mg/kg tid (maximum daily dose 2,400 mg) Adults Dose: 1,200 mg (eight 150 mg capsules) bid <i>NOTE: Adult dosing of amprenavir is now largely in BID combinations with ritonavir at 100mg RTV/600mg APV BID. These doses have not been approved by either the FDA or EMEA and confirming drug levels with TDM in dual PI combinations is recommended in paediatric care.</i>	Amprenavir should not be used in children less than 3 years of age because of the lack of data in children < 3 years of age, the paucity of data in children in general, the uncertain impact of extremely high doses of vitamin E, and the propylene glycol content of the oral liquid preparation (the serum half-life of propylene glycol in neonates is prolonged at 16.9 hours compared to 5 hours in adults). The oral solution and capsule formulation are not interchangeable on a mg per mg basis. The oral bioavailability of the oral solution is 14% less than that of the capsule. Amprenavir may be taken with or without food, but should not be given with a high fat meal (about seven Milky Way bars) as there is a 21% decrease in the AUC when amprenavir is administered after a high fat meal of 67 grams of fat compared with the fasting state. Patients taking antacids (or ddI) should take amprenavir at least 1 hour before or after antacid (or ddI) use.
Indinavir IDV Crixivan®	Capsules: 200, 333 and 400 mg. 100mg capsules expected July 2001 <i>Paediatric formulation (solution) only available in Netherlands.</i>	Neonatal Dose: Unknown. Due to side effect of hyperbilirubinemia, should not be given to neonates until further information is available. Children and Adolescents (4-17yo): 500 mg/m ² (dose adjusted from body surface area (BSA) based on height and weight every 8 hours (see below). Equivalent adult dose of 800mg every 8 hours should not be exceeded. Adult dose: 800mg every 8 hours. <i>NOTE: Adult dosing of indinavir is now largely in BID combinations with ritonavir at 400mg/400mg BID, 100mg RTV/800mg IDV BID, or 200mg RTV/600mg IDV BID. These doses have not been approved by either the FDA or EMEA and confirming drug levels with TDM in dual PI combinations is recommended in paediatric care.</i>	Administer on an empty stomach 1 hour before and 2 hours after a meal (or can take with a light meal). Adequate hydration required to minimise risk of nephrolithiasis (at least 48 oz of fluid daily in adult patients). If co-administered with ddI, give at least 1 hour apart on an empty stomach. Decrease dose in patients with hepatic insufficiency. Capsules are sensitive to moisture and should be stored in original container with desiccant. Blister packs of 400mg now available. Indinavir capsules should only be given to children who are able to swallow hard capsules. Indinavir has not been studied in children under 4 years old.

Drug name	Preparations:	Dosage:	Special instructions:
Lopinavir/r Kaletra ABT-378 Available in UK on named patient basis only. Paediatric dosing based on limited data.	Soft capsules: (133.3mg lopinavir/ 33.3mg ritonavir) Oral solution: 5ml of ABT378/r contains 400mg lopinavir/100mg ritonavir)	Capsules: >2 years with body surface area >1.3m ² is 3 capsules taken twice daily with food. For children with body surface area <1.3m ² use of oral solution is recommended. Adolescent/Adult dose: 3 capsules twice daily. Oral solution: 230/57.5mg/m ² up to a maximum of 400/100mg twice daily. A higher dose of 300/75mg/m ² should be considered when co-administered with efavirenz or nevirapine. Some clinicians prefer this higher dose to be used for all children - as in the M98-940 paediatric study - see pages 10-11 of this report. Adolescent/Adult dose: 5ml (400/100mg) twice daily.	Doses of both formulations should be administered with food. Oral solution dose should be administered using a calibrated syringe. Both formulations can be stored at room temperature for up to six weeks, and refrigerated otherwise.
Nelfinavir Viracept ®	Powder for oral suspension: 50 mg per 1 level gram scoopful (250 mg per 5g scoop); Tablets: 250 mg tablet	Neonatal dose: Recent PK substudies including PENTA 7 (see page 35 of this report) suggested dosing up to 170 mg/kg/day of body weight, split into twice daily doses. <12 months old: 150kg/mg/day split into twice daily doses. Paediatric dose: 50 to 60mg/kg of body weight twice daily. Not to exceed 1250g maximum dose. Adolescent/Adult dose: 1250 mg twice daily.	Administer with meal or light snack. If coadministered with ddl, nelfinavir should be administered 2 hours before or 1 hour after ddl. For oral solution: powder may be mixed with water, milk, pudding, ice cream, or formula (for up to 6 hours). Do not mix with any acidic food or juice because of resulting poor taste. Do not add water to bottles of oral powder; a special scoop is provided with oral powder for measuring purposes. Tablets can be dispersed in water and are used more frequently than the powder. The dispersion can be mixed with milk or chocolate milk; tablets also can be crushed and administered with pudding.
Ritonavir Norvir ®	Oral solution: 80 mg/mL; Soft capsules: 100 mg	Neonatal dose: Under study in Paediatric AIDS Clinical Trial Group protocol 354 (single dose pharmacokinetics). Paediatric usual dose(> 2years): 350 mg/m ² of body surface area every 12 hours. [US guidelines suggest this dose should be 400mg/m ²]. To minimize nausea/vomiting, initiate therapy starting at 250 mg/m ² of body surface area every 12 hours and increase stepwise to full dose over 5 days as tolerated. Paediatric dosage: 350 to 400mg/m ² of body surface area every 12 hours. Not to exceed 600mg BID. Adolescent/Adult dose: 600 mg twice daily. To minimize nausea/vomiting, initiate therapy starting at 300mg twice daily and increase stepwise to full dose over 5 days as tolerated. NOTE: Adult use of ritonavir is now largely as a PK enhancer for a second PI (indinavir, saquinavir, amprenavir). Recommendations for doses these combinations have not been made by either the FDA or EMEA and confirming drug levels with TDM in dual PI combinations is recommended in paediatric care.	Administration with food increases absorption. If ritonavir is prescribed with ddl, there should be 2 hours between taking each of the drugs. Oral solution must be kept refrigerated and stored in original container; can be kept at room temperature if used within 30 days. To minimize nausea, therapy should be initiated at a low dose and increased to full dose over 5 days as tolerated. Techniques to increase tolerance in children: a) mixing oral solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream; b) dulling the taste buds before administration by chewing ice, giving popsicles or spoonfuls of partially frozen orange or grape juice concentrates; c) coating the mouth by giving peanut butter to eat before the dose; or d) administration of strong-tasting foods such as maple syrup, cheese, or strong-flavored chewing gum immediately after dose.
Saquinavir			
Fortovase™ (soft gel capsule)	Soft gel capsules: 200 mg	Neonatal dose: Unknown. Paediatric dose: Soft Gel Capsule: 33mg/kg three times daily. (Currently being studied in PACTG protocol 397). [In children >7 years there is some experience of dual combination with Invirase (hard gel capsule) and ritonavir dosed at 200mg/200/mg BID.]	Administer within 2 hours of a full meal to increase absorption. Concurrent administration of grapefruit juice increases saquinavir concentration.
Invirase™ (hard gel capsule - old formulation)	Hard gel capsules: 200 mg;	Adolescent/Adult dose: Soft gel capsules: 1200 mg three times a day or 1600mg twice daily. Hard gel capsules: 600 mg three times a day; NOTE: Adult dosing of saquinavir is now largely in BID combinations of Fortovase with ritonavir at 400mg/400mg BID. This dose has not been approved by either the FDA or EMEA and confirming drug levels with TDM in dual PI combinations is recommended in paediatric care.	

Note: Body Surface Area (BSA) can be calculated with the following equation:

$$BSA (m^2) = \sqrt{(\text{Height (cm)} \times \text{Weight (kg)}) / 3600}$$

Appendix III: Further reading

US Guidelines for the Use of Antiretroviral Agents in Paediatric HIV Infection, Jan 2000 plus Appendix to Adult guidelines <http://www.hivatis.org>

Principles of management in HIV and pregnancy – Karen Beckerman
Topics in HIV Medicine; Dec 2000 vol 8, issue 7 18-25

Gastrostomy tube (G-tube insertion for improvement of adherence to HAART in paediatric patients with HIV) – Pediatrics 2000, June; 105(6): E80

Medication adherence poor for many HIV-infected children

Pediatric Infect Dis J 2000; 19;1148-1153

Antiretroviral therapy improves thymic output in some HIV-infected children. J Infect Dis 2000; 181 1479-1482

Nutritional support for children with HIV/AIDS – Linda S Heller
<http://hiv.medscape.com/20643.rhtml> (Medscape requires free registration)

What are the special needs of adolescent patients with HIV/AIDS?
http://www.medscape.com/medscape/cno/2000/AAP/Story.cfm?story_id=1777

We report on new findings in paediatric research after each major conference in our monthly review *HIV Treatment Bulletin (HTB)*:

8th Conference on Retroviruses and OIs – Vol 2. No 3, March 2001
<http://www.i-Base.org.uk/publications/bulletins/htb2-3/htb2-3.html>

2nd Intl Workshop on Adverse Reactions and Lipodystrophy/40th ICAAC – Vol 1. No 7 - October 2000, p12/13 & 15 -17, .
<http://www.i-Base.org.uk/publications/bulletins/htb7/htb7.html>

XIIIth International AIDS Conference. Vol 1. No 5 - August 2000 p 7-8.
<http://www.i-Base.org.uk/publications/bulletins/htb5/htb5.html>

7th Conference on Retroviruses and Opportunistic Infection - Vol 1. No 1 - April 2000, p 3-5.
<http://www.i-Base.org.uk/publications/bulletins/htb1/htb1.html>

Appendix VI: TDM Service at Liverpool University

For further information contact Sara Gibbons: Tel: +44 (0) 151 794 5553 Fax: +44 (0) 151 794 5656/5540
email: hivgroup@liv.ac.uk <http://www.hiv-druginteractions.org>

Drug Analysis Available

Protease Inhibitors – Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir

NNRTIs – Delavirdine, Nevirapine, Efavirenz

Others – Sildenafil, Methadone, M8 (nelfinavir metabolite)

Samples - To aid us in the clinical interpretation of the results, it is helpful to have both a trough and a peak sample whenever possible. A trough sample should be taken as close to the end of the dosing interval as possible (i.e. at 12 h for bd regimens or 8 h for tds regimens). A peak sample should be taken approximately 1 h post dose for indinavir alone and 2 h post dose for indinavir with ritonavir and all other drugs. The dosing schedule for efavirenz makes it difficult to obtain trough and peak samples so we will try to give a clinical interpretation for samples from any known time point.

Blood samples should be collected in lithium-heparin tubes (or EDTA if heparinised tubes are unavailable) and plasma obtained by centrifugation within 2 h of collection. The minimum plasma sample volume required is 1 ml per drug analysed, e.g. if a single sample is analysed for saquinavir and ritonavir 2 ml of sample is required. Please do not overfill tubes and allow for expansion on freezing.

Sample Storage - If collection and transport of samples is to occur on the same day, the samples should be kept in a fridge at 4°C prior to transport. If transport is to be later than 24 hours after collection plasma may be stored at -20°C (or lower) and packed whilst frozen and allowed to thaw in transit.

Sample Details - Please complete the sample requisition form with as much information as possible to aid us in the interpretation of the results. Please ensure that samples are anonymised and the full name of the patient does not appear on the form or sample tube. The form is available as a Word 97 document or an Acrobat pdf file.

Transportation - Studies have shown that samples may remain at room temperature for 48 h with no effect on drug levels allowing overnight transportation without the need for packing on dry ice. Please notify us of your intention to send samples so we can ensure prompt handling on their arrival.

Samples may be sent First Class using the Royal Mail so long as all the requirements for the packing of pathological specimens are met. Please post early in the week (Monday–Wednesday) so packages do not remain in the University's mail room over the weekend. UN 602 packaging will be returned to the sender for reuse.

We are a member of the Hays DX system and samples may be sent using the PathPak service (Monday–Thursday). There is no charge to the sending laboratory as all inbound mail on this account is charged to us. This allows departments who are not members of an exchange to send samples from another department without incurring any cost to that department. Packaging will be returned to Hays for redistribution to exchanges.

Cost - The cost of analysis per sample is given below. When samples are analysed for saquinavir and nelfinavir under the scheme sponsored by HIV Focus (Roche Products Ltd), Roche will be invoiced directly for such samples.

Single PI or PI + low dose ritonavir = £40

Multiple PIs = £60

Single PI + single NNRTI = £60

Single NNRTI = £40

Multiple PIs + NNRTI = £90

Please note that when low dose ritonavir is given as a pharmacoenhancer (i.e. <400 mg), no clinical interpretation of the result will be provided and ritonavir will not be classed as PI for charging purposes. When given for antiretroviral activity (i.e. ≥400 mg), a clinical interpretation will be provided and ritonavir will be classed as a PI for charging purposes.

For full pharmacokinetic profiles or large numbers of samples, reduced costs may be available. Please contact Sara Gibbons or David Back to discuss rates.

Results - Samples will be analysed as soon as possible; we aim to send results out within two weeks of receiving the samples. When a fax number is given, results will be faxed and the original sent by second class post. In the absence of a fax number, results will be sent by first class post.

Delivery Address - See delivery address at bottom of form opposite.



Therapeutic Drug Monitoring

Please complete the following details and send with plasma samples to Sara Gibbons at the address below.

Address for Results and Correspondence

Results can also be sent to a secure fax

Contact Details

If we have any queries about this request, please give details of a person we may contact.

Name

Position

Telephone

Fax

E-mail

Patient Information

ID (anonymise)

Date of Birth

Male Female

Weight (kg) Height (m)

Most recent viral load (& date)

Most recent CD4 count (& date)

Drug Therapy

Current Antiretroviral Therapy
(with date started)

Other Medications

Reason for requesting TDM *(tick more than one if applicable)*

- | | | |
|---|---|--|
| <input type="checkbox"/> Possible drug interaction | <input type="checkbox"/> Suspected failure – non responder | <input type="checkbox"/> Paediatric Patient |
| <input type="checkbox"/> Twice daily regimen | <input type="checkbox"/> Suspected failure – rebound | <input type="checkbox"/> Other |
| <input type="checkbox"/> Altered hepatic/renal status <i>(give details)</i> | <input type="checkbox"/> Suspected toxicity <i>(give details)</i> | <input type="checkbox"/> <i>(give details)</i> |

Sample Information

(If patient has previously had TDM, please give our Reference Number.....)

Sample ID	Date taken	Time taken	Drug to be analysed	Dose	Dose Interval	Date of last dose	Time of last dose	Time of last meal

Any other comments *(continue overleaf if necessary)*

ROYAL MAIL
Department of Pharmacology & Therapeutics
University of Liverpool, Ashton Street
Liverpool, L69 3GE

HAYS DX
University of Liverpool (Pharmacology & Therapeutics)
DX 6966700 (TDM Service)
Liverpool 93L

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Tel: 0151 794 5553
Fax: 0151 794 5656/5540
e-mail: hivgroup@liv.ac.uk

Appendix V: Attendee list

Dr Attracta Allen,	Watford General Hospital	Watford
Dr Steven Arpadi,	St Lukes-Roosevelt Hospital,	New York,USA
Joyce Attaro,	Positively Women,	London
Kevin Baker,	Birmingham Heartlands Hospital,	Birmingham
Philip Baker,	Pro-Nexus,	London
Francis Barrett,	St Georges Hospital,	London
Jaqui Baverstock,	Croydon & Surrey Downs NHS Trust,	Croydon
Dr Karen Bekerman,	San Francisco General Hospital,	USA
Catherine Brady,	St George's Hospital,	London
Dean Bright,	HIV i-Base,	London
Kjersti Berrensten,	University Hospital,	Bergen, Norway
Geoff Brand,	Crusaid,	London
Dr David Burger,	Nijmegen Univ. Hosp,	Utrecht, Netherlands
Dr David Burgner,	St Marys Hospital,	London
Edna Chitondo,	North Middlesex Hospital,	London
Margaret Clapson,	Great Ormond Street Hospital,	London
Fiona Clark,	University Hospital of Wales,	Cardiff
Polly Clayden,	HIV i-Base,	London
Simon Collins,	HIV i-Base,	London
Dr Clare Collins,	John Radcliffe Hospital,	Oxford
Rachel Crowther,	Abbott Laboratories Ltd,	Maidenhead
Tara Davis,	Royal Free Hospital,	London
Michael Day,	New Scientist Magazine,	London
Pr. Ronald de Groot,	University of Rotterdam,	Netherlands
Michelle Dawson	Derbyshire Royal Infirmary,	Derby
Sheila Donaghy	St Georges Hospital,	London
AlexDonald	Community Childrens Team,	London
Elaine Dorey	Boehringer Ingelheim,	Berkshire
MariaDowie	Community Childrens Team,	London
CandyDuggan	Redbridge Healthcare Trust,	Ilford
Sophie Elkins	Wiltshire & Swindon Health Care Trust,	Chippenden
Binda Elliot	St Georges Hospital,	London
Wendy Faulkneil	St Georges Hospital,	London
Theresa Fisher	Newham Community Health Care Trust,	London
Dr Lisa Frenkel	University of Washington,	USA
Paul Foster	HIV i-Base,	London
Dr Carlo Giaquinto	PENTA, Padua,	Italy
Dr Diana Gibb	MRC Clinical Trials Unit,	London
Kirsty Gillibrand		London
Dr Gurbindo Gutierrez Colores	Hospital Infantil Gregorio,	Madrid, Spain
Dr Jennifer Handforth	St Georges Hospital,	London
Di Hart	London Borough of Camden,	London
Thandi Haruperi	Blackliners,	London
Geoffrey Henning	Roche Products,	Welwyn
Jane Hewitt	St Georges Hospital,	London
Ian Hitchcock	Abbott Laboratories,	Maidenhead
Michelle Holder	Watford General Hospital,	Watford
Christine Hubbock		Bristol
Dr Margaret Hudson	Medicines Control Agency,	London
Bob Huff	American Foundation for AIDS Research,	USA
Mohamade Jowata	Parkside Health Trust,	London
Quinley Julian	THT/ATP,	London
Annabel Kanabus	AVERT,	Horsham
Liz Kawonza	Terrence Higgins Trust,	London
Denzil Kennedy	THT/ATP,	London
Dr Saye Khoo	University of Liverpool,	Liverpool
Douglas King	Chelsea & Westminster Hospital,	London
Chi Ko	The Jarman Centre,	Blackburn
Portia Kumalo	North Middlesex Hospital,	London
Sandra Laird	Abbott Laboratories,	Maidenhead
Rebecca Lubega-Bukulu	Young Peoples Health Cnc,	Mile End Hosp, London
Carol Lennie	Royal Hospital for Sick Children ,	Edinburgh
Michael Luckett	THT/ATP	London
Dr Hermione Lyall	St Mary's Hospital	London
Badru Male	Blackliners	London
Janet Masters	Institute of Child Health	London
Sarah Masters	MRC -London	London
Laura McGee	MRC CTU	London
Kamie McLennan	St Georges Hospital	London
Dr. Jeanette Meadway	Mildmay Mission Hospital,	London
Ann Maria Medford	North Manchester Healthcare NHS Trust,	Manchester
Zuber Mitchla	Royal Free Hospital	London
Dr Claus Moller	University Hospital,	Bergen, Norway
Karen Moshal	Royal Free & University College Medical School,	London
Esther Moshinghi	Positively Women	London
Cephas Mosinghi	Africare	London
Andrew Moss	HIV i-Base	London
Sharon Muhammad	Islington Council Social Services,	London
Lorna Murray	Abbott Laboratories	London
Simon Mwendapole	Blackliners	London
Dr Daya Nayagam	South London NHS Trust- Specialist Services,	London
Dr David Newsom	Northwick Park Hospital,	Harrow
Monica Ngoshi	Blackliners	London
Ian Nixon	North Manchester Health Care Trust,	Manchester
Bridgit Noack		London
Gail Noel-Keith	South London Community Health,	London
Dr V Novelli	Great Ormond Street Hospital,	London
SonjaNueske	St Georges Hospital	London
Mary Okoth	Positively Women	London
Dr A Pahari	St Marys Hospital	London
Nina Panahmand	Mortimer Market Centre,	London
Tanya Parr	i-Care	London
Pr Catherine Peckham	Institute of Child Health,	London
Clare Penny	Children with AIDS Charity,	London
Mike Phillips	THT	London
Vivian Pribram	Forest Healthcare Trust	London
Dr Octavio Ramilo	UT Southwestern Medical Centre - Dallas,	USA
Rebecca Rebuga-Bukulu	Tower Hamlets Healthcare Trust,	London
Dr Anna Riddell		Oxford
Ian Robertson	PositiveSupport - Edinburgh,	Edinburgh
Dr A Sarmah	QEQM Hospital - Margate,	Kent
Dr Liesbeth Scholunck	St Marys Hospital,	London
Dr VinitShah	William Harvey Hospital	Kent
Dr Mike Sharland	St George's Hospital	London
Dr Delane Shingadia	Royal London Hospital	London
Marianne Silvester	St Georges Hospital	London
Sharon Storey	St Georges Hospital	London
Lynne Taylor	St Georges Hospital	London
Peter Tovey	S. Essex Community Health Trust,	Essex
Sue Trickett	Great Ormonde St Hospital,	London
Themoulla Troulidou	Dupont Pharmaceuticals Ltd,	Stevenage
Dr Annmarie van Rossum	Sophia Childrens Hospital,	Rotterdam,Netherlands
Pr Stefano Vella	Instituto Superiore di Sanita,	Rome, Italy
Dr Alessandra Viganò	Clinic Paediatrica IV, Hosp. L Sacco,	Milan, Italy
Carole Vincent	Young Peoples Health Cnc,	Mile End Hosp, London
Alain Volny-Anne	Sol En Si, Paris	France
Carol Wallace	Community Childrens Team,	London
Jo White	St Mary's NHS Trust	London
Matthew Williams	The Monument Trust	London
Sue Yeadon	East Oxford Health Centre	Oxford

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