Paediatric HIV infection: correlates of protective immunity and global perspectives in prevention and management

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The impact of the HIV epidemic on child health globally is beginning to be appreciated. With the burden of new infections falling on young women, there is a skyrocketing number of AIDS orphans, and a rapidly increasing number of children infected via mother-to-child-transmission (MTCT). An estimated 600,000 new paediatric infections occur each year, of which some 1500/day (> 90%) occur in sub-Saharan Africa. But whereas children account for only 4% of those currently living with HIV infection, 20% of AIDS deaths have been in children. This reflects the rapid progression to disease in paediatric HIV infection. Whereas a dramatic reduction in viraemia follows acute adult infection, corresponding to the appearance of a vigorous anti-HIV cytotoxic T lymphocyte response, virtually no impact of the immune response is observed in acute paediatric infection following MTCT. Two specific challenges for the paediatric immune response are: (i) infection occurs before the immune system itself is fully developed; and (ii) the viruses transmitted by MTCT have already evaded an immune system sharing close genetic relatedness to that of the child. Accumulating evidence indicates that the immune system is potentially capable of effective control of HIV infection, and that events occurring in acute infection critically determine the ultimate outcome. Technological advances that have transformed the study of T-cell immunity now enable the developing immune system in childhood to be better understood. Via novel immunotherapeutic approaches described, it may be possible to modulate the infant’s immune response to reach effective and durable suppression of HIV, as can be achieved by the rare long-term non-progressors of HIV infection. The feasibility of adopting these approaches globally are as yet untested. Finally, the striking

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disparity between the burden of paediatric HIV infection and access to the necessary infrastructure and therapeutic options required for its optimal management is addressed in a comparison between three sites of paediatric HIV care: Durban, South Africa; London, UK; and Boston, USA.

In 1998, an estimated 5.8 million new HIV infections occurred worldwide, of which 10% were in perinatally infected children. The figures are similar for the years 1999 and 2000. This translates into more than 1600 infants newly infected each day. But only 4% of the world’s population who are currently infected with HIV are children, whereas 20% of the AIDS deaths have been in children. This reflects the rapid progression to disease that is a hallmark of paediatric HIV infection, especially in the non-industrialised world where access to antiretroviral therapy is limited at best. Approximately 90% of the 3 million live children infected are in sub-Saharan Africa, where the HIV prevalence in antenatal clinics was typically between 15–30% in the mid-1990s and today approaches 50% in the worst-hit regions. Even taking into account the potential impact of prophylactic antiretroviral therapy instituted peripartum, and other approaches – notably influencing infant breast-feeding patterns – to reduce mother-to-child-transmission (MTCT), it is likely that 10–15% of children born to infected mothers will be infected. In the children who are not perinatally infected with HIV, the incidence of new infection when they reach teenage begins to rise rapidly, up to levels of 20% per year for women aged 20–24 years. Avoiding exposure to HIV infection in some regions of the world is extremely difficult. The clear and logical conclusion is that an HIV vaccine that is effective in early childhood is most vitally needed.

The first part of this review will focus on the extent of our understanding to date of what constitutes protective immunity against HIV in paediatric infection and how these research studies might translate into effective new immunomodulatory approaches or vaccine design in the future. The second part of the review describes the practicalities of preventing paediatric infection and of managing children infected with HIV. The approaches available in the non-industrialised world are contrasted with those in countries such as the US and the UK, where there is accessibility to highly active antiretroviral therapy (HAART) in paediatric infection.

**Natural history of paediatric HIV infection**

Perinatally infected children generally progress to disease more rapidly than infected adults. Early studies of perinatally infected children,
before the era of HAART, from the European Collaborative and US groups indicated that a subset of approximately 25% of perinatally infected children progress very rapidly to AIDS within 1 year. The median time to AIDS for the remaining 75% was approximately 7 years. Recent data from a cohort in Malawi appear to indicate an even more dismal prognosis for perinatally infected children in parts of sub-Saharan Africa, with 89% mortality by 3 years of age\(^1\). Since the median age at enrolment was 8 months, by which time a proportion of infants would have already died (the recorded infant mortality being only 7%), it is possible that this figure of 89% may even underestimate the impact of HIV on childhood mortality in the first 3 years of life. Some of the more dramatic and intriguing data from this study are that the majority of the infected children died in the short period between 2.0 and 2.7 years of age. Whether HIV infected children progress more rapidly to disease and death as a result of HIV per se in non-industrialised countries than they would do in industrialised countries in the absence of antiretroviral therapy it is only possible to speculate. A recent review argued that adult HIV-1 infection progresses to disease no more rapidly in Africans than in industrialised nations\(^1\). However, the observation that infants are more vulnerable than adults to HIV disease is beyond dispute. Importantly, the reasons for this are not yet established.

### Successful control of HIV in adult infection

The immune system is capable of effective control of chronic virus infections such as herpes virus infections and HIV. Whereas successful containment of chronic herpes virus infections is the rule, control of HIV is exceptional. However, a very small subset of HIV-infected persons have now been infected for over 20 years with successful suppression of virus. Early studies revealed that cytotoxic T lymphocytes (CTL) play a central role in reducing HIV replication, both by killing virus-infected cells and by the production of antiviral factors\(^1\). A critical difference between the immune response towards HIV in ‘long-term non-progressors (LTNP)’ and the ‘progressors’ is that anti-HIV T helper activity is required to enable CTL to maintain suppression of virus long-term\(^1\).

Investigators in Boston recently set out to determine why the majority of HIV-infected adults fail to control virus long-term\(^1\). It was reasoned that, during acute infection, T helper cells are specifically targeted by the virus and thus in most cases rapidly become eliminated; and that early institution of highly active antiretroviral therapy (HAART) would protect against this loss of T helper cells. Acutely infected adults were, therefore, recruited and treated immediately with HAART. The T helper responses in these early-treated subjects reached very high levels, similar
to those in LTNP subjects. However, since HAART had so quickly switched off virus replication, the CTL responses in this group were relatively low. After stopping HAART for short periods, the CTL responses increased substantially, and the T helper responses were augmented even further. At this stage, it was possible for these subjects to discontinue HAART altogether and yet maintain control of HIV to low levels for more than a year.

The value of these studies in terms of the global epidemic are 3-fold. First, the view that HIV infection inevitably leads to AIDS and death is discredited, since, with the appropriate immune responses intact, control of the virus by the immune system is clearly possible. Second, the specific immune responses that are associated with effective containment of HIV are identifiable more clearly as the CTL and T helper responses. Third, the acute immune response as key20–29 is underlined. Similar interventions in chronically infected adults have not had measurable impact30. The next step is to expand on these studies of B clade HIV infection in the US and apply the work to C clade infection dominating the sub-Saharan African and the growing Asian epidemics31,32.

**Mechanisms of progression to disease at different rates**

The causes of HIV pathogenesis in adult as well as paediatric infection are not well understood. In adult infection, as described above, Gag-specific T helper activity and CTL activity33 have been associated with successful control of viraemia. But what determines whether some individuals maintain the critical helper responses whilst the majority lose them in acute infection? Factors unconnected with the immune response such as chance, the amount of virus transmitted, the fitness of the transmitted virus, and host genetic factors affecting viral entry all may play a role34,35. However, a strong clue that specific components of the immune response play an important part in determining HIV outcome derives first from the finding that HLA class I homozygosity is strongly associated with more rapid progression to disease36; and, second, from the associations of particular class I molecules with slow or rapid progression35.

The class I molecule that stands out as being associated with rapid progression is HLA-B3536,37. Detailed analysis of this effect revealed that the commonest subtype, B*3501, is not in fact associated with rapid progression, and the association with rapid progression comes from the strong effect of the less common subtypes37. Structurally, the difference between these subtypes lies in the size of the residue that can be accommodated in the F pocket of the peptide-binding groove, into which binds the C-terminal anchor residue of the B35-binding peptide.
HLA-B*3501 has a more capacious F pocket and preferentially binds large residues such as Tyr in this C terminal anchor position of the peptide. The less common subtypes of B35, such as B*3502 and B*3503, carry smaller F pockets only capable of binding smaller residues. One can hypothesise that there is less choice in the peptides that can bind to B*3502 and B*3503, since small residues can be accommodated within a large pocket in the peptide-binding groove, with water molecules adequately filling the remaining space available.

The class I molecule most strongly associated with slow progression in HIV infection is HLA-B57. In this case, again, the F pocket admits a large residue, preferentially Trp. Notably, HLA-B57 is able to bind peptides of quite variable lengths, from 8-mers to 11-mers, whereas the class I alleles associated with rapid progression such as B35 or B8 tend to bind shorter peptides of 8 or 9 amino acids in length only. Closely related to B57 is HLA-B*5802, a subtype that would be expected to have difficulty accommodating Trp in C-terminal position of the peptide. HLA-B58 is, interestingly, not associated with slow progression from preliminary studies. HLA B57 and B58 are important in sub-Saharan Africa since, in HIV-affected populations such as Zulu, South Africa, 35–40% of persons express one or other of these class I molecules. Further studies are needed to test this hypothesis, that a large choice in peptide is important in mounting an effective response to a virus such as HIV.

An alternative hypothesis to explain the association of particular class I molecules with slow progression is that, by chance, the immunodominant epitopes that are targeted happen to be situated in regions of fundamental importance to viral fitness. One good example of this is the HLA-B27-restricted epitope in p24 Gag, KRWIILGLNK (KK10). With very few exceptions, all B27-expressing adults so far studied generate a strong response to this epitope KK10. This is sometimes the only detectable HIV-specific response. HLA-B27 is associated with slow progression in adult infection. Thus the mechanism of this association of slow progression is may be through this KK10-specific response. Loss of recognition of the KK10 epitope arises through mutation in the anchor position 2 in the B27-binding peptide: this position has to be occupied by Arg for adequate binding to B27. The mutations arising in this normally highly conserved epitope are largely restricted to persons with B27 and arises late in the infection.

This epitope lies in the centre of the helix-7 that forms the interface between one p24 molecule and its partner in the formation of the homodimeric p24 Gag structure. Loss of this homodimeric structure leads to failure of new virion formation. It happens that a mutation in the second position of the KK10 epitope involves a residue that is critically participating in the homodimer binding. In fact this mutation...
does not appear to be accommodated within this helix-7 in the absence of other compensatory mutations developing previously. In some instances, these compensatory mutations arise elsewhere within the KK10 epitope, in others they occur far outside the epitope in the linear sequence but very close within the p24 structure. Thus the association of B27 with slow progression may derive from the chance happening of the dominant epitope being situated in a region of critical importance to viral replicative fitness.

Studies to characterise further the role of CTL escape in HIV pathogenesis need to be undertaken in persons expressing alleles such as B8 and B35 that are associated with rapid progression and comparative evaluations made of CTL escape in persons expressing alleles such as B27 and B57 that are associated with slow progression. The most illuminating data will come from investigations of acute infection where, as described above, the immune events to a great extent set the ultimate course for the infection as a whole. However, identification of acute HIV infection in adults is problematic unless there are symptoms, and emerging evidence is that adults with acute infection who express HLA-B27 or HLA–B57 are less likely to present with acute HIV syndrome. One may hypothesise that effective B27- and B57-restricted CTL responses are generated early in acute infection, bringing about more rapid control of viraemia and reducing symptomatic acute infection. In contrast, B8- and B35-restricted responses may arise later or may be easily evaded by immune escape, in either case failing to bring about effective early control of virus replication (Fig. 1). The limited data available support this hypothesis. What is beyond dispute is that quite distinct CTL specificities may operate in acute

![Diagram](image_url)

**Fig. 1** Schematic view of hypothesised changes in viral load, HIV-specific CTL and T helper cell responses during the course of HIV infection in slow and rapid progression. Viral load shown in log_{10} RNA copies/ml plasma.
Specific problems in control of paediatric HIV infection

There are two particular problems for children infected with HIV. The first is the timing of infection, in that in the great majority of cases transmission occurs perinatally and, therefore, at a time when the immune system is not fully developed. If, as indicated above, T cell immunity plays the central part in successful containment of HIV, and the critical time for an effective immune response to kick in is in acute infection, then the infected infant is very vulnerable to HIV infection around the time of birth. An immature immune response would certainly fail to contain the virus, and would also expose the thymus to HIV-mediated destruction, as has clearly been observed. Studies of the effectiveness of the neonatal immune response in humans to perinatal virus infection have not been made, however, largely because of the unavailability of assay systems sensitive enough to obtain useful information from small amounts of blood. The advent of Elispot and flow cytometry-based assays (reviewed by Goulder) has transformed what is now possible in studies of childhood T cell immunology.

The second particular problem for children infected with HIV is that the virus is transmitted from their mother. The degree of HLA class I
sharing between mother and child is higher than might initially be appreciated since, for a given allele expressed in the mother, the chances are only as low as 50% if the prevalence of that allele in the population is < 0.5% (Fig. 2). For alleles that have a frequency of as high as 25%, such as A*0201 in many Caucasoid populations, the chances of a mother with that allele sharing it with her child is > 80%. This is because there is a substantial chance of the mother being homozygous for that highly frequent allele, and also because the child also has a high chance of inheriting that same allele from the father. Furthermore, it is certain that the child will share at least 3 of the 6 HLA-A, HLA-B and HLA-C class I molecules expressed by the mother, whereas the chances that any individual shares more than one allele with an unrelated person is low – the precise likelihood depending on the particular alleles expressed by the mother. The potential significance of this HLA class I sharing between mother and child is that virus that has evaded the maternal HLA class I restricted CTL response will already be equipped to evade the child’s CTL response, since the identical epitopes would be targeted by the child’s immune response.

In order to determine whether this HLA sharing is actually significant in limiting the CTL activity against HIV available to children infected by MTCT, we investigated further the HLA-B27-KK10 response described above which has been associated with protection against progression to disease in adult infection. Comparison of the frequency with which HIV-infected children and infected adults with B27 target this KK10 epitope showed a significant difference, with > 85% of adults (19/22 studied) targeting this epitope and only 33% (2/6) children with B27 showing responses to this epitope (P = 0.02, Fisher’s exact test). When the virus in the non-responding children was compared with the virus present in the mothers, in each of the 3 cases where the mother and the child shared B27, the same KK10-escape sequence (Arg to Thr in each instance) was also common to the mother and child. In the single case where transmission to a child with B27 occurred from a mother who was B27-negative, there was no mutated KK10 epitope transmitted. That child in fact resembles an adult with HLA-B27, since at 7.8 years of age he is a long-term non-progressor, with a CD4 count of > 800 cells/mm³, strong p24 Gag-specific T helper activity (data not shown) and an undetectable viral load since first measured at 4 years of age (< 400 or < 50 RNA copies/ml plasma) on ddI/AZT therapy. This is exceptional by paediatric standards, with levels this low seen in only 5/130 infected children being treated at The Children’s Hospital, Boston out-patient clinics (Burchett S and McIntosh K, personal communication).

Thus, there are additional challenges to the immune system in perinatal HIV infection to those that are posed by HIV in adult infection. As described above, the early immune events are critical to the outcome
from HIV infection. An effective and multifaceted early CTL response is likely to be the key to limiting the damage that occurs to the immune system in acute infection. Evasion of this early CTL response by epitope mutation is one of the principal methods by which the virus can maintain a foothold and inflict this irreparable damage. Work to compare the timing and role of escape in the adult and infant is underway, but from the preliminary data that are available, one may hypothesise that CTL escape plays a far more extensive part in preventing the paediatric immune response from containing early viraemia (Fig. 3). Two principal reasons for this, as described above, may be the immaturity of the paediatric immune response at the time of infection and the transmission of preformed CTL escape viruses from the HLA class I sharing mother. Determining the relative importance of these two factors in the more rapid progression to disease that is observed in paediatric infection is vitally important, as the approaches to achieving successful containment of HIV in paediatric infection depend on first understanding the cause of failure to control viraemia.

**Augmenting HIV-specific immunity in paediatric infection**

The ultimate goal for the prevention of paediatric HIV infection is an effective vaccine that can be administered at birth. Even then, it may be
envisioned that this vaccine would be needed to be given in conjunction with a period of HAART in infected neonates in order to prevent the immune destruction that follows persistently high levels of viral replication. In the absence of a vaccine, similar approaches to the one that has been utilised so effectively in acute adult infection in the US may be adopted. In the case of paediatric as opposed to adult acute infection, there is the great advantage that it is possible to anticipate early infection in infants by antenatal testing of mothers. Having determined whether MTCT has occurred by determining plasma viral RNA levels in the first 1–2 months of life, HAART may be instituted with the goal of limiting to a minimum any HIV-mediated damage to the developing immune system. This can be achieved in the setting of the US healthcare system, as demonstrated by Luzuriaga and colleagues. As the understanding of which particular antiretroviral drugs are suitable for use in infants, and as formulations of the drugs are developed to facilitate adherence, it may be possible to construct effective regimens of HAART that can be adopted also in non-industrialised countries for infected infants. This will buy a period of time during which the developing immune system is protected from HIV-mediated damage, and during which the immune system itself can mature to generate a more effective suppression of viraemia. At this point, HAART may then be discontinued for short periods of supervised treatment interruption (STI) to enable the infant’s immune response against the virus to be boosted, but with HAART restarted before viraemia can reach the levels at which damage can be done, in particular to the developing virus-specific T helper responses. The long-term aim of this approach would be to augment the virus-specific immunity sufficiently via these STIs to enable HAART ultimately to be discontinued altogether. One particular advantage of STI as a form of autovaccination is that the immune system is being boosted with the autologous virus sequence. The theoretical disadvantage is that, having cleared viral reservoirs of virus via long-term HAART, that these will be filled rapidly by STI. However, against this there is now strong evidence that viral reservoirs are never completely eradicated by HAART, either in adult or paediatric infection.

An alternative method of inducing HIV-specific immunity in infected children whose virus is suppressed by HAART is to use HIV vaccines. A variety of candidate HIV vaccine approaches are presently being developed (reviewed by Letvin et al.). Other forms of immunotherapy currently being developed include the infusions of peptide-pulsed dendritic cells to induce primary CTL responses, and approaches using inactivated whole virus vaccines specifically designed to induce HIV-specific T helper activity. However, the distinction should be emphasised again between interventions that are made in children or...
adults whose immune systems have been protected by HAART instituted in acute infection, as opposed to HAART instituted in chronic infection, after the damage of acute infection has been done. Also, it is expected that attempts to boost T helper activity in chronic infection will be fruitless in the absence of effective HAART cover73.

In summary, the options available to augmenting anti-HIV immunity in paediatric infection are growing, although their accessibility in countries worst afflicted by the epidemic at present are limited and even in industrialised countries progress is at an early stage. However, the transformation of what is possible in studies of T cell immunity has been so startling over the past 2–3 years that dramatic advances in our understanding of neonatal and older paediatric T cell immunity are likely rapidly to follow. These will inevitably bring new approaches to supplement those promising immunotherapeutic avenues already being developed.

**Prevention of paediatric HIV infection**

Prevention of paediatric HIV infection has centred until very recently on the belief that HAART is unaffordable for people infected with HIV in non-industrialised countries. Prophylactic drugs used in pregnancy or simply in labour4 are effective in reducing MTCT. The use of a single drug, nevirapine, that is given once to the mother and once to the newborn child, in reducing MTCT by close to 50% is difficult to argue against at $4 a treatment. However, high prevalence of HIV infection in children depends particularly on two factors – high prevalence of HIV in antenatal mothers, and high viral loads in the antenatal mothers. The peripartum administration of nevirapine reduces the viral load to which the new-born is exposed by ensuring therapeutic drug levels in the baby during the first few days of life. However, these therapeutic drug levels are only maintained for a few days, and this intervention neither protects fully against peripartum MTCT, nor at all against post-partum (breast-milk) transmission. The MTCT rate remains in the region of 10–15% in spite of prophylactic nevirapine. Clearly more needs to be achieved.

One intriguing approach being developed in Durban, South Africa by Coutoulidis and colleagues74 is the idea that exclusive breast-feeding might reduce MTCT. Most studies (for example see Dunn et al75) previously described the risk of breast milk transmission without reference to the feeding pattern of the infant, in particular whether breast-feeding was exclusive or mixed with formula or other forms of nutrition. The initial observations in Durban7 were that the rate of MTCT was 18.8% in children whose mothers did not breast feed, was 24.1% in children whose mothers mixed breast- and other feeding, and
was only 14.6% in the children whose mothers exclusively breast-fed for > 3 months. The mothers in these different groups did not differ in their viral loads or CD4 counts. These data appeared to be inconsistent with a concurrent study by Miotti et al in Malawi, but this latter study did not distinguish between exclusive and mixed breast-feeding. Further studies with longer follow-up are underway. However, a distinctly sobering caveat to any recommendation that HIV-infected mothers should exclusively breast-feed has emerged from work in Kenya, where a greatly increased mortality was observed in mothers who breast-fed. As many as 69% of the deaths observed in HIV-infected mothers could be attributable to breast-feeding alone. This cost to HIV-infected mothers who are evidently at the limit of their metabolic reserves is an additional factor that clearly needs to be fully taken into account before the optimal infant feeding patterns can be determined.

Equally controversial is the issue of availability of HAART for all adults and children infected with HIV. Clearly, HAART accessibility would have a huge impact on preventing paediatric infection for at least two reasons. Transmission between adults as well as from mother-to-child is more likely in the setting of a high viral load in the donor, and thus reducing viral load via HAART would be likely not only to reduce the prevalence of HIV in antenatal mothers but also to reduce the viral load in those infected mothers throughout pregnancy. This might be expected to reduce MTCT by closer to 67% than the 47% reported for nevirapine alone.

Is making HAART available for all infected persons worldwide a realistic prospect? Certainly Attavan and Sachs have served to highlight how little assistance is being given towards dealing with the problem of the global HIV epidemic, and how static this level of support has remained (approximately $200 million per year in total development assistance from 1994–1998, latest figures available) in the face of the rapidly expanding numbers of HIV infection. These authors estimate that to treat 10 million infected persons with HAART would cost $5 billion a year, provided drugs can be obtained at ~5% of the usual costs of $10,000 per person per year. Whether this can be achieved remains to be seen. Suffice it to say that this appears to be a new option that has hitherto been overlooked, and one that would have a real chance of making a significant impact on the global epidemic, while work to develop vaccines and other immunomodulatory approaches can continue apace.

Management of paediatric HIV infection

The contrast between management of paediatric infection in resource-rich countries and resource-poor countries could not be more stark.
While this relates in part to access to HAART, it reflects also the disparity in the infrastructure and supportive networks that underpin paediatric HIV management in countries such as the US, where there are perhaps 200 new cases of perinatally acquired HIV infection each year,
and in countries such as South Africa, where the figure would be currently approximately 75,000 per year. The differences in infrastructure and management are summarised in Tables 1–3. The most striking differences in the management of HIV infected children relate to the disparity between burden of infection and infrastructural support (Table 1). It should be noted that King Edward VIII Hospital (KEH) in Durban is distinctly one of the better equipped hospitals in sub-Saharan Africa, and that even more striking disparities would have been evident had a rural hospital in sub-Saharan Africa been included in the comparisons. Although at KEH prophylaxis against MTCT is available in the form of nevirapine in labour and to the child in the first 3 days of life, this is only available currently at a handful of localities in South Africa – hence the wide range in estimated newly infected children in South Africa of between 40,000 and 75,000 each year, depending upon accessibility of nevirapine. Less apparent than might be expected in the KEH is the real impact of HIV in the adult community on AIDS orphans in Africa, with as many of 40% of children attending the clinic being looked after at home by biological parents. However, this may be due to selection bias, with children having living parents more liable to be brought to the KEH clinic.

The clinical presentation of paediatric HIV infection at the three sites is summarised in Table 2, and perhaps the major differences being the broader spectrum of clinical presentation patterns in Durban. This may be reflective of the larger numbers of infected children seen in Durban, and also of the higher background morbidity in the Durban population, with

<table>
<thead>
<tr>
<th>Age of child</th>
<th>King Edward VIII Hospital, Durban, South Africa</th>
<th>St Mary’s Hospital, London, UK</th>
<th>The Children’s Hospital, Boston, USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>&lt; 2 months: congenital TB, CMV, syphilis</td>
<td>PCP, FTT, neurodevelopment</td>
<td>PCP, FTT, neurodevelopment</td>
</tr>
<tr>
<td></td>
<td>2–6 months: PCP, HSM, chronic gastroenteritis,</td>
<td>regression, CMV retinitis,</td>
<td>regression</td>
</tr>
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<td></td>
<td>candidiasis</td>
<td>refractory candidiasis</td>
<td></td>
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<tr>
<td></td>
<td>6–12 months: FTT, recurrent LRTIs, thrush,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>chronic diarrhoea, neurodevelopment delay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toddler age group</td>
<td>Lymphoid interstitial pneumonitis (LIP), TB,</td>
<td>Persistent adenopathy ± HSM,</td>
<td>Persistent adenopathy</td>
</tr>
<tr>
<td></td>
<td>chronic gastroenteritis, recurrent bacterial</td>
<td>Persistent adenopathy ± HSM,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sepsis (skin/ears/chest), zoster, malignancies</td>
<td>Persistent adenopathy ± HSM,</td>
<td></td>
</tr>
<tr>
<td>Older children</td>
<td>recurrent LRTI, LIP, bronchiectasis, chronic lung disease, TB, otitis media, impetigo, CNS infection – toxoplasmosis, cryptococcal meningitis</td>
<td>Asymptomatic (family member diagnosed), recurrent LRTI, LIP, bacteraemia, zoster, candidiasis, (MAI/PCP end-stage)</td>
<td>PCP, oral candidiasis, MAI, zoster, recurrent severe HSV</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; PCP, Pneumocystis carinii pneumonia; HSM, hepatosplenomegaly; FTT, failure-to-thrive; LRTIs, lower respiratory tract infections; LIP, lymphoid interstitial pneumonitis; MAI, Mycobacterium avium intracellulare; HSV, herpes simplex virus.
Table 3  Clinical management of paediatric HIV infection at each study site

<table>
<thead>
<tr>
<th>Stable patients doing well</th>
<th>King Edward VIII Hospital, Durban, South Africa</th>
<th>St Mary’s Hospital, London, UK</th>
<th>The Children’s Hospital, Boston, USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of follow-up</td>
<td>1–2 monthly</td>
<td>3 monthly</td>
<td>2 monthly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 4 monthly: also TG/cholesterol (if on PI)</td>
<td>• 4 monthly: also TG/cholesterol (if on PI)</td>
</tr>
<tr>
<td>Patients starting therapy or changing therapy</td>
<td>Monthly</td>
<td>2, 4 and 8 weeks after start; (also 6 weeks if NVP) then 2–3 monthly</td>
<td>2, 4 and 8 weeks after start; monthly until VL &lt; 50; then 2 monthly</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>• PCP: all children of HIV +ve mothers until 1 year; continue if clinically indicated</td>
<td>• PCP: all children of HIV +ve mothers until third PCR +ve (at 4 months); prophylaxis until CD4 &gt; 15%</td>
<td>• PCP: CD4 &lt; 200 or CDC cat 3 or 12 months of age</td>
</tr>
<tr>
<td></td>
<td>• Anti-TB prophylaxis if TB contact; INH + rifampicin for 3 months after excluding TB</td>
<td>• MAA/HIV/HSV/ZVF/fungal: rarely used only if CD4 &lt; 5% and unresponsive to new HAART</td>
<td>• MAAI: CD4 &lt; 75 or CDC cat 3</td>
</tr>
<tr>
<td></td>
<td>• Ketoconazole (for recurrent candidiasis)</td>
<td>• Most common prophylaxis: valaciclovir for recurrent shingles</td>
<td>• Fungal: fluconazole for CDC category 3 symptoms</td>
</tr>
<tr>
<td>Treatment</td>
<td>AZT/3TC or ddI/dd4T</td>
<td>• Initial: 2 NRTIs + 1 NNRTI (NVP or EFV)</td>
<td>• Initial: 2 NRTIs + PI/NNRTI (PI usually NFV; NNRTI either NVP or EFV)</td>
</tr>
<tr>
<td>What drugs are used?</td>
<td></td>
<td>• High VL: 3 NRTIs (AZT/3TC/ABC) + NNRTI (NFV or EFV)</td>
<td>• High VL: 2 NRTIs + PI + NNRTI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Change: 2 new NRTIs + PI (Kaletra)</td>
<td>• Change: res testing + 2 new NRTIs/2 PIs or 2 new NRTIs/NNRTI/PI(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Salvage change: res testing + e.g. new PI + NNRTI</td>
<td>• Salvage change: res testing + new PI + NRTIs, NNRTI if susc, 2 new PIs (res testing)</td>
</tr>
<tr>
<td>Treatment</td>
<td>If drugs can be afforded by parents of children symptomatic of HIV infection</td>
<td>All new diagnoses, if parents willing Symptomatic older children or CD4 &lt; 25% or falling CD4%</td>
<td>All new infant diagnoses Aim for: normal immune system or VL control</td>
</tr>
<tr>
<td>Who is treated?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% patients not on ART</td>
<td>&gt; 95% (&gt; 228/240 not on HAART)</td>
<td>&gt; 29% (&gt; 34/118 not on HAART)</td>
<td>&gt; 0% (&gt; 5/130 on only NRTIs)</td>
</tr>
<tr>
<td>Monthly IVIG</td>
<td>0%</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Gastrostomy tubes</td>
<td>0%</td>
<td>3%</td>
<td>5% (for medication)</td>
</tr>
</tbody>
</table>

Antiretroviral drugs: NRTIs, nucleoside analogue reverse transcriptase inhibitors; AZT, zidovudine; 3TC, lamivudine; ABC, abacavir; NNRTIs, non-nucleoside analogue reverse transcriptase inhibitors; NVP, nevirapine; EFV, efavirenz; PI, protease inhibitors, Kaletra; NFV, nelfinavir; IDV, indinivir; RTV, ritonavir; SQV, saquinavir; APV, amprenavir.

Investigations: FBC, full blood count; Diff, differential; U&E, urea and electrolytes; LFT, liver function tests; VL, viral load; CD4, T-cell subsets.
factors including overcrowding, limited access to fresh water supplies, and malnutrition contributing to the higher frequency of TB, CMV, gastroenteritis and other infectious disease seen in this population.

Clinical management of infected children at the three sites are summarised in Table 3. As expected, although clinical follow-up is very frequent in Durban and long-term follow-up of children attending the clinic at KEH is exceptionally complete, more investigations are undertaken in the management of children cared for in the UK and in the US, where many more treatment options are available, in particular of course antiretroviral therapy.

Conclusions

The impact of HIV on childhood health world-wide is becoming increasingly apparent. Children infected with HIV progress rapidly to disease for reasons that are not fully established. The immune response mediated through CTL and T helper cell activity plays a central role in control of HIV in adult infection. Technical obstacles to investigating the immune response in infants have been to a large extent overcome by access to Elispot and flow cytometry-based assays, and these on-going studies should bring significant advances to our understanding of the specific problems encountered by the immune system of the neonate and infant confronted by MTCT of HIV infection. Preliminary data would indicate that there is a particularly strong rationale to adopting one or more of a variety of novel immunotherapeutic approaches to augment these HIV-specific T-cell responses in paediatric infection. Considerable challenges would lie in the way of the delivery of any new approach, including antiretroviral therapy itself, to dealing with HIV infection at the site of the epidemic. However, since the critical events determining the course of infection may be concentrated at the very early stages of infection, effective interventions or treatments of short duration can be envisaged that could have a major positive impact on the global paediatric epidemic.

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References

25. Pantaleo G, Demarest JJ, Schacker T et al. The qualitative nature of the primary immune response to HIV infection is a prognosticator of disease progression independent of the initial level of plasma viremia. Proc Natl Acad Sci USA 1997; 94: 254–8
30 Oxenius A, Price DA, Phillips RE. Unpublished data
40 Miguelles SA, Sabbaghian MS, Shupert WL et al. HLA-B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long-term non-progressors. Proc Natl Acad Sci USA 2000; 97: 2709–14
42 Barber LD, Percival L, Arnett KL, Gumperz JE, Chen L, Parham P. Polymorphism in the α1 helix of the HLA-B heavy chain can have an overriding influence on peptide-binding specificity. J Immunol 1997; 158: 1660–9
43 Goulder PJR, Tang Y, Pelton SI, Walker BD. HLA-B57-restricted CTL activity in a single infected subject towards two optimal HIV epitopes, one of which is entirely contained within the other. J Virol 2000; 74: 5291–9
the Twelfth International Histocompatibility Workshop and Conference. Paris: EDK, 1997; 345–53
49 Goulder PJR, Phillips RE, Colbert R et al. Late escape from an immunodominant cytotoxic T lymphocyte response associated with progression to AIDS. Nat Med 1997; 3: 212–7
53 Mear JP, Schreiber KL, Munz C et al. Misfolding of HLA-B27 as a result of its B pocket suggests a novel mechanism for its role in susceptibility to spondyloarthropathies. J Immunol 1999; 163: 6665–70
59 Altfeld M. Unpublished data
69 Finzi D, Blankson J, Siliciano JD et al. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. Nat Med 1999; 5: 512–7
73 Kahn JO, Cheng DW, Murray H, Lagakos S. Evaluation of HIV-1 immunogen, an immunologic modifier, administered to patients infected with HIV having 300 to 549 x 10(6)/L CD4 cell counts: a randomized controlled trial. JAMA 2000; 284: 2193–202
76 Miotti PG, Taha TE, Kumwenda N et al. HIV transmission through breastfeeding – a study in Malawi. JAMA 1999; 282: 744–9
78 Editorial. Grants, not loans, for the developing world? Lancet 2001; 357: 1