Paediatric HIV grows up: recent advances in perinatally acquired HIV

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ABSTRACT

This review is an update focusing on the current status of paediatric HIV in the UK and Ireland. Successes in prevention of mother to child transmission are highlighted. The changing epidemiology of the UK cohort is summarised and the shift in emphasis of treatment guidelines beyond limiting short-term morbidity and mortality to ensuring optimal health status in adult life is discussed. Current and future challenges relating to an aging cohort, successful transition to adult services and the prospect of a lifetime on antiretroviral therapy (ART), as well as the possibility of ART-free survival are also considered. While numbers of HIV-infected children in the UK are now decreasing, lessons we have learned in the last 30 years from this relatively small cohort are increasingly applicable to the global paediatric HIV population.

INTRODUCTION

Childhood HIV infection and AIDS remain a global challenge. In 2012, approximately 260 000 (230 000–320 000) children under the age of 15 years were diagnosed with HIV, bringing the total number of children estimated to be living with HIV to 3.3 million (3 million–3.7 million). The estimated number of AIDS-related deaths in this age group was 210 000 (190 000–250 000). The vast majority of new infections in children occurred in sub-Saharan Africa, a reflection of the overall burden of HIV infection in women of childbearing age and limited coverage of interventions targeted at prevention of mother to child transmission (PMTCT).[1]

HIV transmission from mother to infant can occur antenatally, intrapartum or postnatally.[2] The risk of vertical transmission can be reduced from as high as 40% with no intervention to <0.5% in developed countries by implementing measures including appropriate antenatal antiretroviral therapy (ART), intrapartum ART, elective caesarean section in cases with detectable maternal viral load (VL), early neonatal postexposure prophylaxis and exclusive formula feeding.[3]

In resource-poor settings, PMTCT strategies differ from those in developed countries, employing a more public health-based approach adapted to the needs of populations with dramatically different health infrastructure, drug availability, laboratory monitoring facilities and breastfeeding practices.[4] Transmission rates are higher in these countries than in resource-rich areas.[5] Furthermore, multiple factors contribute to suboptimal implementation of recommended interventions with a number of sub-Saharan African countries having PMTCT coverage rates of <50%.[1] It is hoped that these shortfalls in access to PMTCT will be addressed through a new programmatic, public health-based approach, whereby all HIV-infected pregnant women commence and remain on ART for life.[4]

ART dramatically reduces morbidity and mortality in children;[6] however, access to ART is limited in many countries with the highest requirement. Access for those children in need of ART was estimated to be only 34% (31%–39%) globally in 2012. Difficulties in early diagnosis of HIV infection, rapid disease progression and problems in developing appropriate drug formulations for children all contribute to coverage figures that are frequently worse than those observed for adults in the same geographical region.[1]

Despite increasing rates of new paediatric HIV infection in some regions of the world (for example, the Middle East and North Africa), worldwide rates are dropping. The death rate due to childhood AIDS is decreasing and the overall number of children living with HIV has levelled off.[1] Elimination of mother to child transmission is now considered to be an achievable goal (UNAIDS definition of elimination is a perinatal transmission rate of <2%).[7] There is a shift in focus beyond ensuring survival into adulthood, towards optimisation of health status throughout childhood and adolescence in preparation for healthy and productive adult life.

As access to ART is increasing in resource-poor settings, numbers of children surviving into adolescence are also expanding. The problems currently affecting HIV-infected adolescents in resource-rich settings such as the UK, many of whom had access to antiretroviral therapies immediately following licensing, are increasingly relevant globally.[8] Furthermore, teams responsible for the health of the relatively small number of HIV-infected children in the UK can learn much from those looking after the expanding numbers of older children now surviving in areas such as sub-Saharan Africa.

CURRENT STATUS OF PAEDIATRIC HIV IN THE UK AND IRELAND

Current European guidelines provide recommendations on when to commence ART in HIV-infected children based on clinical, immunological and virological criteria.[9] Standard first-line therapy consists of a three-drug regimen including either a boosted protease inhibitor or a non-nucleoside reverse transcriptase inhibitor with two nucleoside/nucleotide reverse transcriptase inhibitors. The main aim of treatment is undetectable HIV RNA in blood and a CD4 count in the normal range. Once ART is initiated, it should be continued for life, the main

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risks of long-term therapy being drug toxicity and development of drug resistance.

In 1989, the National Study of HIV in Pregnancy and Childhood (NSHPC) was established for the UK and Ireland. This is a confidential national reporting scheme for pregnancies in HIV-infected women (through obstetric services), babies born to HIV-infected women and other children with HIV infection and AIDS (through the British Paediatric Surveillance Unit (BPSU)). The NSHPC collects demographic data and limited follow-up information on HIV-exposed and HIV-infected children.[10] In 2000, the Collaborative HIV Paediatric Study (CHIPS) was established to collect data on children treated in Paediatric European Network for Treatment of AIDS (PENTA)-associated centres in the UK and Ireland.[11] CHIPS currently collects long-term clinical and immunological data on all HIV-infected children reported to the NSHPC.[10 11] The number of children under NSHPC/CHIPS follow-up steadily increased until around 6 years ago when numbers plateaued at around 1300 and have subsequently decreased (figure 1). This can be mainly attributed to the introduction of combination ART as standard therapy for children in 1997, recommendation of routine antenatal HIV testing for all pregnant UK women in 2000 and effective implementation of PMTCT protocols resulting in a reduction in the rate of vertical transmission for babies born in the UK to <0.5%[3 6](figure 2). Since the introduction of combination ART for children, there has been a substantial decrease in the mortality associated with paediatric HIV infection.[6] The age distribution is shifting upwards (figure 3), and the number of children transitioning to adult services is increasing.[13]

The immunological and virological status of HIV-infected children in the UK has improved year-on-year. Of the children in active CHIPS follow-up with available data, 85% have a CD4 percentage >20% (<15% is classified as severe immunosuppression (US Centers for Disease Control and Prevention (CDC) categories)). Of those children on ART in 2010, 83% had a VL of <400 c/mL and 70% had a VL of <50 c/mL on two separate occasions (these two VL cut-offs have both been used to define 'undetectable' VL, although the latter is more commonly used currently in the UK).[13] This is approaching but not yet equivalent to the estimated proportion of ART-treated HIV-infected adults with VL <50 c/mL in 2011 (approximately 88%).[12]

PREVENTION OF MOTHER TO CHILD TRANSMISSION

Through multidisciplinary collaboration and a highly proactive approach, the UK PMTCT programme has resulted in unprecedented low levels of new perinatal infection.[3] But it should be noted that onward transmission still occurs both in the context of missed maternal diagnosis *and* through rare failures of PMTCT in mothers diagnosed antenatally. Reasons for failure of antenatal screening include both maternal and health service factors. Missed diagnoses through failure of reporting positive testing, seroconversion during pregnancy and maternal refusal to test have all been reported.[14] As maternal refusal is a possible risk factor for HIV infection, UK practice regarding procedures for when a mother has refused testing in pregnancy is a subject of current national audit. A paediatric team involved in the care of a baby whose mother has refused antenatal testing should consider the increased risk of HIV transmission in this situation and discuss postnatal testing of the baby while seeking advice from a specialist centre. Rarely, transmission has occurred following a negative HIV test in early pregnancy, presumably as a result of in utero, perinatal or breast milk transmission following maternal infection late in pregnancy. Feasibility of selective repeat screening in third trimester in high-prevalence areas is under consideration, although not currently recommended.[15] Transmission has also occurred despite antenatal diagnosis in the context of a diagnosis made late in pregnancy, premature delivery or presumed early in utero transmission. It is hoped that through analyses of each case of transmission in much the same way as a 'serious incident, processes can be improved to bring overall transmission rates as low as possible.

THE UK PAEDIATRIC HIV COHORT IN 2014

The majority of UK HIV-infected children have vertically acquired HIV-1 infection. Of the 1131 children currently under CHIPS active follow–up, 52% are female, 51% were born abroad, 79% are of black African and 50% are followed up in a London clinic. The median age has increased from 5.1 years in 1996 to 13.6 years in 2012. The number of new cases presenting per year has reduced to only 44 in 2011[13] with only nine known incidents of mother to child transmissions in women known to be HIV infected prior to delivery in the years 2010–2011 (n=1975, transmission rate=0.46%).[3] New cases

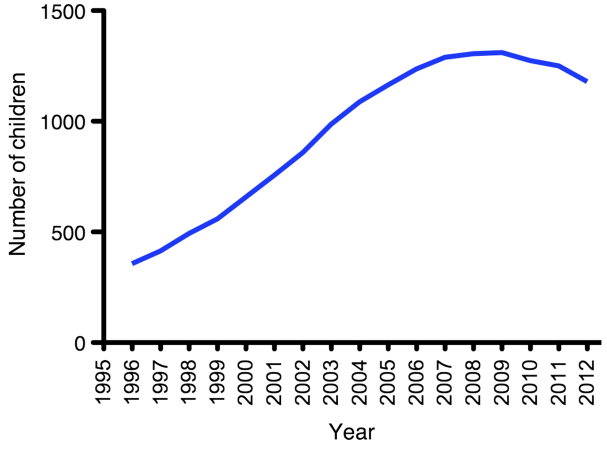

Figure 1 Number of HIV-1-infected children registered in National Study of HIV in Pregnancy and Childhood/Collaborative HIV Paediatric Study (NSHPC/CHIPS) follow-up in the UK and Ireland by year (adapted from Collaborative HIV Paediatric Study report 2013 (with permission)).[12]

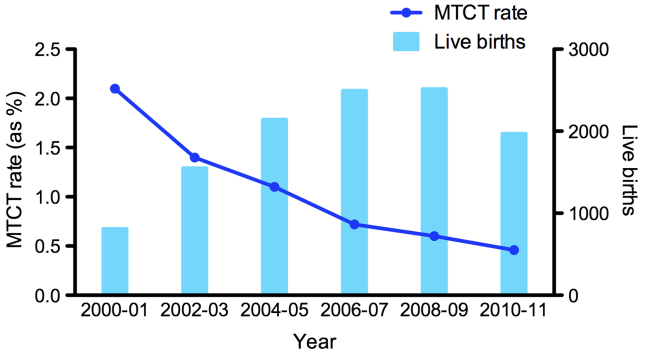

Figure 2 Trends in UK and Ireland mother to child transmission (MTCT) rates over time. The transmission rate was significantly lower in 2007–2011 (0.57%, 33/5788, 95% CI 0.39% to 0.80%) than in 2000–2006 (1.2%, 71/5727; p<0.001). The apparent decline in the number of births is mainly a result of delay in reporting of infection status for children born 2010–2011 (adapted from Townsend *et al* 2014 (with permission)).[3]

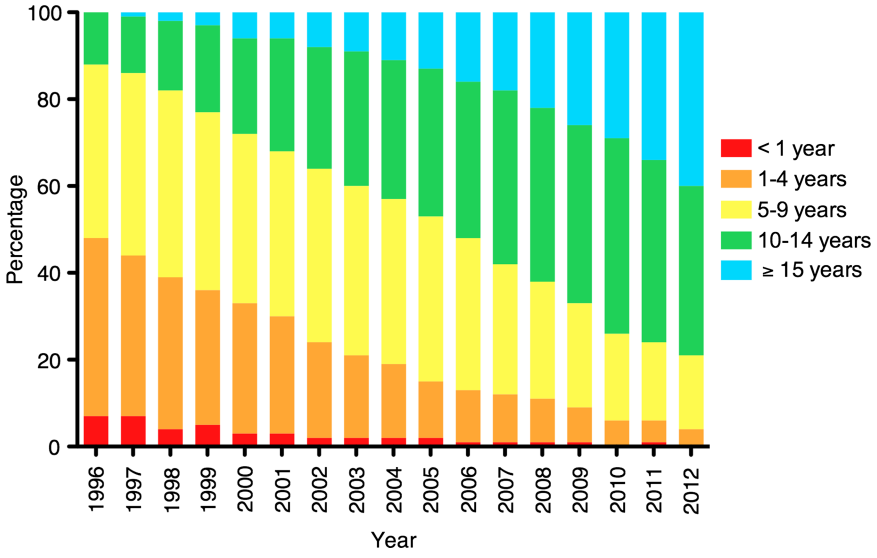

Figure 3 Age distribution of HIV-1-infected children in National Study of HIV in Pregnancy and Childhood/Collaborative HIV Paediatric Study (NSHPC/CHIPS) follow-up in the UK and Ireland by year (adapted from Collaborative HIV Paediatric Study report 2013 (with permission)).[12]

presenting to medical services are mainly diagnosed through screening of asymptomatic children at risk of HIV infection (ie, following diagnosis of a relative or following failed PMTCT) or occasionally through testing of children presenting with clinical signs of HIV. Of approximately 400 children reported to the NSHPC 2009–2013, around three-quarters were born outside the British Isles. Information about whether they were diagnosed before arrival was not available for a quarter. Where information was provided, just under half were diagnosed prior to their arrival (Pat Tookey (NSHPC), personal communication). Newly immigrant HIV-infected children already on ART require urgent medical referral to ensure continued adequate supply and dosing of medications and to allow baseline clinical assessment. Of note, a retrospective audit of children diagnosed over the age of 13 years found approximately half to be *asymptomatic*, emphasising the importance of testing any child or young person at risk of HIV irrespective of age and symptoms.[16]

As the UK cohort has aged, the emphasis of care has now shifted to the management of adherence, complex resistance, transition of care to adult services, long-term drug toxicity and sexual and mental health.[17 18] Issues of fertility are becoming relevant as the older adolescents enter young adulthood with completed pregnancies now reported in young women with perinatally acquired HIV.[19]

STRUCTURE OF CARE SERVICES: PRESENT AND FUTURE

Paediatric HIV services in the UK have benefitted from organised national data collection on almost all children born to HIV-infected mothers and HIV-infected children in medical care in the UK (BPSU, NSHPC, CHIPS). Historically, the highest numbers of patients were focused in London and as a result, the largest and longest running clinics remain in this location. As children and their families have become more dispersed throughout the UK, clinics with smaller cohorts of children and less multidisciplinary resources have been established. The need for networks of expertise to support practice in smaller centres was recognised, resulting in the development of the Children's HIV National Network in 2005.[20] A tiered system whereby local centres are supported by regional networks, which are in turn supported by three London lead 'hubs', has led to regular sharing of knowledge and multidisciplinary resources through outreach clinics, regional and national meetings.

Another great asset to children's HIV services in the UK and Ireland has been close collaboration with the voluntary sector.

Table 1 Comparison of current immunological, virological and clinical thresholds for antiretroviral therapy initiation in HIV-infected children

	WHO 2013	DHHS 2014	PENTA 2014
<1 year	All	All	All
1–3 years	All *Prioritise*: 1–2 years WHO stage 3/4 CD4≤750≤ 25%	CD4<1000<25% CDC category B/C VL>100 000 c/mL *Consider*: All	CD4≤1000≤25% CDC category B/C *Consider*: All VL>100 000 c/mL
3–5 years	All *Prioritise*: WHO stage 3/4 CD4≤750≤25%	CD4<750<25% CDC category B/C VL>100 000 c/mL *Consider*: All	CD4≤750≤25% CDC Category B/C *Consider*: VL>100 000 c/mL
>5 years	CD4≤500 *Prioritise*: WHO stage 3/4 CD4≤350	CD4<500 CDC category B/C VL>100 000 c/mL *Consider*: All	CD4≤350 CDC Category B/C *Consider*: All *CD4≤500* VL>100 000 c/mL

Further clinical criteria (coinfection, end organ damage, etc.) are omitted for simplicity.[4 9 22]
CD4 count units, cells/μL; CDC, US Centers for Disease Control and Prevention; DHHS, US Department of Health and Human Services; PENTA, Paediatric European Network for Treatment of AIDS; VL, HIV viral load.

The Children's HIV Association (CHIVA: http://www.chiva.org.uk) and HIV in Young People Network (HYPNet: http://www.hypnet.org.uk) provide support and resources for health professionals, social care, voluntary sector and children and families living with and affected by HIV. Educational and motivational activities involving peer support such as the annual CHIVA support camp (http://www.chiva.org.uk/camp) have proven highly successful in bringing together otherwise isolated HIV-infected children from all over the UK, allowing them to meet, form lasting friendships and learn from other HIV-infected young people.

Increasing limitations on resources make running multidisciplinary services for complex long-term conditions, such as paediatric HIV, more difficult. However, the national service specification for children and young people with HIV[21] makes it clear what should be provided and what families should expect. With the small number of patients widely dispersed across the country, there is a difficulty in resolving tension between keeping services as local as possible and providing a full team approach. In many cases, this is addressed by having a local paediatric team sharing care with a regional multidisciplinary team.

ADVANCES IN ART

Since the advent of ART, 'when to start' and 'what to start' have been the subject of ongoing debate informed by data from large cohort studies, extrapolation from adult data and a small number of randomised trials. The pendulum has swung from recommending early treatment, to delaying treatment until clinical or immunological criteria are met, to starting all infants irrespective of immune status, to considering treatment for all.[4 9 22] Current WHO, US and PENTA treatment thresholds are compared in table 1.

The reason for this evolution in practice in resource-rich settings stems in part from a change in goals of care. Initially survival was the main focus. Then followed limitation of drug toxicity. Presently, while these two aspects of care are still important, survival is almost guaranteed with appropriate ART treatment in these settings. Toxicity, being less with newer drugs, can be managed with appropriate monitoring and regimen modification. The focus of current US and European guidelines is on optimising immune status and neurodevelopment, minimising development of resistance and limiting the potential effects of ART toxicity in adult life. Data from adult and paediatric studies are accumulating, supporting the idea that starting ART prior to deterioration in CD4 count has the potential to ensure maximal immune reconstitution and to minimise irreversible effects of HIV on immune development.[23] National and international guidelines have recently been updated bearing this in mind. In addition, strong evidence for prevention of onward sexual transmission of HIV while on suppressive ART has led to inclusion of 'treatment as prevention' in current adult guidelines.[24] With the ageing of the paediatric cohort, the importance of including this as a potential indication to start treatment in adolescents should be acknowledged.

Availability of ART and licensing processes for children have historically lagged behind those of adults. However, the tide has turned. The armoury of available HIV drug classes and hence possible combinations for first, second and subsequent line therapies have expanded (integrase inhibitors, CCR5 receptor antagonist, next-generation non-nucleoside reverse transcriptase inhibitors). Trials of paediatric formulations and pharmacokinetic (PK) studies in children are integral in the licensing process for new drugs for adults. Previous paediatric ART treatment guidelines were largely based on extrapolation from adult data and, out of necessity, recommended a number of drugs outside of their licence. Recently updated guidelines have the luxury of having the option to incorporate a larger range of drugs that is almost equivalent to those available in adult practice, down to all but the youngest ages.[4 9 22]

But obstacles still remain. Drugs may now have appropriate formulations licensed down to young ages (efavirenz sprinkles, chewable raltegravir), but conflicting data on PK and limited clinical experience of the use of drugs in the paediatric age range make it essential to use caution when incorporating into new guidance. Children grow rapidly and once-daily fixed dose combinations (FDCs) are unavailable at younger ages. Construction of regimens that are easy to adhere to, ensure adequate drug levels and minimise pill burden and the chances of developing resistance are ongoing challenges below 12 years of age. Drug metabolism is faster in younger children and once-daily treatments for older children and adults may not be sufficient for under 5s, highlighting the importance of PK data for all age groups. With the completion of trials such as CHAPAS-3, it is hoped that FDCs for younger children will become available (http://www.controlled-trials.com/ISRCTN69078957).

New antiretrovirals are more expensive than older drugs and generic formulations are now becoming available. This inevitably impacts upon the cost-effectiveness of drug regimens. Guidelines, while considering the strengths and weaknesses of existing clinical data, must also take into account financial restraints of their target populations. UK paediatricians on the whole follow the PENTA treatment guidelines.[9] When treatment decisions are more complex, for example, in the context of triple class resistance, comorbidity, difficult adherence, complex toxicity, high-cost drugs or coinfection, it is recommended that cases are discussed in a 'virtual clinic' including specialist pharmacist, virologists, adult physicians, as well as paediatric infectious disease specialists.[25]

Regarding frequency of monitoring, the results of the ARROW trial, undertaken in Africa, have demonstrated that a reduction in the frequency of laboratory monitoring is possible and safe while on ART.[26] Current guidelines reflect this, with recommendations for less frequent monitoring of CD4 count and drug toxicity.[4 9 22] Current PENTA guidelines provide recommendations for minimum frequency of laboratory monitoring in children both on and off ART, with CD4 monitoring being prioritised prior to ART initiation and VL monitoring emphasised once established on therapy. However, at times of treatment failure, switch in ART, suspected drug toxicity and when approaching treatment thresholds, it is recommended that frequency of laboratory monitoring should be increased accordingly.[9] It is hoped that a reduction in the number of unnecessary, expensive tests will reduce costs and allow diversion of funding towards medication costs and multidisciplinary care.

NOT ALL PLAIN SAILING: LESSONS TO BE LEARNED

The UK cohort has clearly benefited from early access to ART, with 50–100 adolescents per year now transitioning to adult services.[13] The management of this transition of care has become a major focus of UK paediatric HIV services, resulting in them having to rapidly adapt to the needs of adolescents during this often difficult phase of their life. Following the move to adult services, challenges still remain in the management of these young adults, a proportion of whom were diagnosed in pre/early ART era. Triple class resistance,[27] long-term drug toxicity, psychopathology,[28] complex adherence issues (often starting in early life), learning difficulties/neurodisability and poor

retention in care can all add to patient complexity. Older ART-treated children can have subtle yet significant neurodevelopmental deficits with risk of more severe impairment in those with a history of severe disease, high VL or abnormal brain imaging.[29]

Regarding toxicity, strategies to reduce cumulative drug exposure such as structured treatment interruption[30 31] and short cycle therapy (http://clinicaltrials.gov/ct2/show/NCT01641016) have been explored. In contrast to the SMART trial in adults,[32] treatment interruption has been shown to be a safe strategy in children. However, rates of restarting ART are high and evidence of immune activation during interruption is a cause for concern.[33] Planned treatment interruption is therefore not currently recommended.

Rates of metabolic disturbances (dyslipidaemia, insulin resistance) and body fat abnormalities (lipoatrophy, lipohypertrophy) are significant in older children with perinatally acquired HIV.[34] Reports of body image issues and associated corrective cosmetic surgery are starting to emerge.[35] Unexpected delayed toxicities from first-generation antiretrovirals are also reported. Worryingly, the known association between ART, didansosine, in particular, and non-cirrhotic portal hypertension in adults, has now been reported in the context of perinatally acquired HIV.[36] Long-term implications of this unusual complication, predictors of risk and the utility of focused screening are yet to be determined. While deaths still occur for various reasons including advanced AIDS, bronchiectasis and suicide, it is of note that it is very rare for an individual with perinatally acquired HIV to die in the UK with untreatable HIV infection.[18]

With earlier, presymptomatic diagnosis and treatment, improved adherence support, less toxic drugs in easier to use formulations and increased awareness of long-term psychosocial needs, it is hoped that younger HIV-infected children today can look forward to a future when HIV has much less impact on their health status. The Adolescents and Adults Living with Perinatal HIV Cohort study (http://www.ctu.mrc.ac.uk/research_areas/study_details.aspx?s=258) is a UK-based observational cohort study currently recruiting children aged 13–21 years with perinatally acquired HIV alongside uninfected young people of the same age. Its aim is to investigate the long-term impact of HIV and ART on neurocognitive function/psychosocial issues, heart disease, metabolic function, sexual health and growth. It is hoped that through recruitment of extremely well-matched controls, confounding factors will be minimised and real effects of HIV on the health of this expanding age group will be determined and used to guide treatment of younger children.

Stigma and maintaining secrecy of their diagnosis is still very much part of the lives of HIV-infected children and adolescents. HIV-infected young people themselves are increasingly taking on this challenge. Through the use of media campaigns (Children in Need, TV interviews, websites) and social media (http://www.twitter.com/freedom2spk), they are raising awareness among their peers in the hope that future generations will not have to face the levels of prejudice that have confronted previous generations.

PROBLEMS OTHER THAN TOXICITY ON ART

With the trend towards earlier commencement of ART and with efforts to increase access, the large majority of HIV-infected children should eventually be on ART, with a high proportion having an undetectable VL. However, there are issues to consider in addition to long-term drug toxicity. As in adult HIV infection,[37] there is mounting evidence that ongoing immune activation occurs even in the context of fully suppressive ART.[38 39] The precise mechanism is still not clear, although translocation of microbial products such as lipopolysaccharide from the gut, homeostatic response to lymphopenia, irreversible alterations in structure of lymphoid tissue and direct and indirect viral effects through alteration of the cytokine milieu and cell–cell signalling have all been implicated.[37] The long-term implications of ongoing immune activation are unclear but could result in a sustained increase in cardiovascular risk, neuroinflammation and risk of malignancy.

A FUTURE FREE OF ART?

International excitement surrounded the recent news of an infant who, having initiated ART very early after birth, achieved persistent HIV viral suppression despite ART interruption.[40] Although this child has subsequently relapsed and has restarted ART,[41] this case along with reports of sustained viral suppression in several adults following ART cessation[38] has reignited interest in possible strategies to remove the need for long-term ART. Replication-competent HIV persists in certain cells (viral reservoirs) even after long periods of time on fully suppressive ART.[42] The role of minimisation of these reservoirs in order to maximise the potential for immune control or eradication of HIV has been highlighted. Emerging data indicate that early ART treatment, during primary infection in adults or in the first few days after birth in infants, may be associated with lower viral reservoirs.[43 44–46] It is possible that those with lower reservoirs may be more amenable to future 'curative' therapies. The UK-based Cherub collaboration (http://www.cherub.uk.net) is investigating the effects of early treatment as well as the role of various other treatment strategies in reducing reservoirs in order to explore the possibility of HIV remission or eradication. The use of bone marrow transplant[47] and gene therapy, resulting in replacement of the recipients CD4 compartment with cells resistant to HIV infection, is another exciting field, although it will only be of use under very rare specific circumstances, such as coexistent malignancy.

CONCLUSION

HIV-infected children are growing up. As numbers of new infections decrease and older adolescents graduate to adult services, it is essential that services evolve to address the cohort's changing needs. HIV-infected babies born today, although fewer in number, will require specialist paediatric HIV care for at least the next 16 years. It is vital that new drugs, novel drug formulations and alternative treatment strategies are made available to young people as and when they need them. Smaller patient numbers will limit individual centre experience. Ongoing national and international collaboration through clinical trials and sharing of knowledge through courses such as those coordinated by PENTA (http://www.penta-id.org/education/trainforpedhiv.html) will be essential for future success. Where once our treatment aim for children with HIV was to prevent death, our focus now is on optimising health for adulthood so that young people are placed optimally for 'curative' treatment as and when it becomes available.

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