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Cover: *Children from a Cape Town community attend an HIV prevention event (photo by Keren Middelkoop). Another photo taken at the event appears inside this issue. Sandy Bailey took the photos of children from Gugulethu enjoying the delights of a Cape Town beach on a Sisanda FunDaytion outing, and Yvonne Budig the photo of the sleeping baby.*

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PUBLISHERS
SAMA Health & Medical Publishing Group
Tel: (021) 681 7200
Article submissions: www.sahivmed.org.za

FOR MORE INFORMATION CONTACT
SA HIV CLINICIANS SOCIETY
Suite 233, PostNet Killarney
Private Bag X2600, Houghton, 2041
www.sahivsoc.org
E-mail: sahivsoc@sahivsoc.org
Tel: +27 (0) 11 341 0162
Fax: +27 (0) 11 341 0161

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FROM THE EDITOR

No, I am not on sabbatical on a tropical island! However, it has been a great pleasure to have the *Journal* guest-edited again for the last edition of 2009 by a superb duo: Leon Levin and Mark Cotton.

Mark Cotton is a specialist in paediatric infectious diseases at Tygerberg Children's Hospital and head of its Paediatric Infectious Diseases Unit, affectionately known as Kidcru. His main focus is to extend and enhance care through research, with a special interest in children affected by HIV. Mark has been involved in some key studies that have shaped paediatric practices and guidelines in southern Africa. He also serves as advisor and investigator to a number of international institutions and networks.

Dr Leon J Levin graduated MB BCh at the University of the Witwatersrand in 1987. After training in paediatrics at the Wits group of hospitals in Johannesburg, he obtained his FCPaed (SA) in 1994. In February 1996 he founded the Paediatric HIV Clinic at Johannesburg Hospital, and more recently he has run the paediatric division of Right To Care. Leon has been Chairman of the Paediatric Subcommittee of the SA HIV Clinicians Society since 1999 and runs the Society's Paediatric Discussion Group, an Internet-based forum for paediatricians to discuss and learn about problems in children with HIV.

In this edition, besides a fabulous array of paediatric material, we publish the updated paediatric guidelines. With so much positive energy around better HIV support recently, from the highest level, we are confident that we can do better, especially in the important area of paediatric AIDS.

We will kick 2010 off with our usual diverse submitted copy, so please keep sending. Review processes will also be improved. We hope it will be a bumper year in many ways, with record numbers of people starting and staying on ART, a decreasing incidence of HIV, and millions of South Africans testing. We also hope to have four bumper editions of the Southern African Journal of HIV Medicine in 2010, which is set to be a memorable year for South Africa.

LINDA-GAIL BEKKER
Editor

EDITORIAL

TREATING HIV-INFECTED CHILDREN

This edition sees the publication of the fourth SA HIV Clinicians Society paediatric antiretroviral therapy (ART) guidelines. Previously it has not been possible to have one guideline for the whole country because of wide discordance between the government and private sectors. This year, for the first time, our guideline is applicable to both the private and public sectors. Inevitably some differences remain and are addressed in the document. They include choice of first-line regimen and genotyping recommendations. The national Department of Health (NDoH) is still updating its guidelines, hopefully for publication in early 2010. We hope you will find the Society's guidelines pragmatic and helpful. We have the potential to save and improve many young lives.

We thank all those involved in the writing of the guidelines, especially our fellow member of the writing committee, Dr Tammy Meyers, and our overseas reviewers.

As has been done previously when paediatric guidelines have appeared, the entire issue is devoted to paediatrics. We hope it will be useful as a ready reference on paediatric HIV management for all health care workers caring for children.

We begin with an opinion piece by Heather Jaspan, Rachel Li, Leigh Johnson and Linda-Gail Bekker on the urgent need to develop skills and infrastructure to meet the needs of HIV-infected adolescents, especially given our success in treating children with ART.

We then address prevention of vertical transmission of HIV, the key to the elimination of HIV infection in children. The paper by Laurie Schowalter, Ashraf Coovadia and Ameena Goga is a plea for action. It is followed by an analysis of vertical transmission data (Mark Cotton, Soyeon Kim, Helena Rabie, Joan Coetzee and Sharon Nachman, from the PACTG 1041 team), emphasising again the importance of a good antenatal antiretroviral component. Infant feeding is integral to child survival and development. There are risks and benefits for breast and replacement feeding. The paper by Ameena Goga is essential reading for anyone caring for infants and provides the key data to inform rational decision making.

The guideline document emphasises the importance of and pitfalls in maintaining adherence. A number of articles provide background information to help in understanding the rationale of recommendations in the guidelines. These include articles on when to start (Mark Cotton, Helena Rabie, Ute Feucht and Avy Violari), essential pharmacokinetic information (Helen McIlleron and Hermien Gous) and how the weight-based dosage recommendations were derived (James Nuttall).

What do you do when children starting ART deteriorate instead of improve? Helena Rabie, Tammy Meyers and Mark Cotton delve into the paradoxical world of immune reconstitution inflammatory syndrome (IRIS).

We then highlight two adverse events of ART, one common and the other rare.

The NDoH guidelines do not advocate using abacavir (ABC) in the first-line regimen in the absence of adverse effects from other drugs. They still recommend d4T, increasingly implicated in lipodystrophy. Lipodystrophy can be reversible if the offending agent (usually d4T) is replaced with ABC (or tenofovir in adults) in the early stages. Steve Innes, Leon Levin and Mark Cotton provide background information and useful diagnostic and management advice for lipodystrophy.

The SA Clinicians Society advocates 3TC and ABC as the NRTI backbone for the first-line regimen. There is much fear of the infamous ABC hypersensitivity reaction (HSR). To the best of our knowledge, no one has ever died from the reaction, but people have died from ABC rechallenge. Fortunately the HSR is rare in black Africans. Helena Rabie, Kristin Henning, Pierre Schoeman, Nico de Villiers, Gert H J (Oubaas) Pretorius and Mark Cotton provide guidelines for using ABC and recount their experience with suspected ABC HSR.

Treatment failure is becoming increasingly complex. Fortunately, there are quite a few new antiretrovirals registered overseas and about to be registered in South Africa. Leon Levin takes us through the minefield of paediatric salvage therapy.

Finally, Polly Clayden presents us with some cutting-edge reports from the recent International AIDS Society Conference in Cape Town, again informing readers of the type of research needed to continually improve our guidelines.

MARK COTTON
LEON LEVIN
Guest Editors

MESSAGE FROM THE EXECUTIVE

The global recession has thrown the problem of funding for AIDS programmes to the fore, with Botswana's president saying his country's programme is unsustainable, and donors sounding warnings that rationing may need to be implemented. This is very alarming – we have made big strides in terms of antiretroviral access in the last few years, and these are suddenly looking very fragile.

It is time to take stock of our programmes and make them as lean and mean as possible, ensuring maximum access to care while ensuring acceptable levels of quality. We need to look critically at the labs we ask for and the drugs we need, while keeping up pressure on the donor community to maintain support.

However, we should not let our governments off the hook. Health in southern Africa has been consistently underfunded as a function of the gross domestic product, in almost every one of our countries. Guns, presidential inaugurations and motorcades never seem to be a problem to fund, and we need to do a better job at

drawing attention to how health budgets are allocated. In South Africa it seems that Jacob Zuma's government has declared war on overall wasteful expenditure, and at the same time there has been increasing embarrassing public exposure of ministerial spending on large cars. A new and energetic health minister, Aaron Motsoaledi, seems intent on reversing the terrible sins of the past under Mbeki's regimen, and to be determined that health resources get used better.

Please let the Society know if you see any indication of rationing! We have active advocacy work, with good partners, and it is to be hoped that we can stop unnecessary restrictions on health care.

FRANCOIS VENTER
President

MESSAGE FROM THE PAEDIATRIC SUB-COMMITTEE

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY PAEDIATRIC DISCUSSION GROUP (PDG)

The Southern African HIV Clinicians Society Paediatric Discussion Group (PDG) began in December 2001. The concept was born after Dr (now adjunct Professor) Ashraf Coovadia of the Rahima Moosa Mother and Child Hospital, Coronationville, Johannesburg, sent an e-mail to 5 or 6 local HIV 'experts' and Professor Mark Kline of the Baylor College of Medicine, Houston, Texas, seeking advice on how to manage a child with severe disfiguring parotomegaly but who had a normal CD4 count, so antiretroviral therapy (ART) was not indicated. The answer came back that there was no indication for ART for a purely cosmetic condition!

I found the concept fascinating and wondered if there was any value in using e-mails as a vehicle for educating health care providers about paediatric HIV. I contacted the South African HIV Clinicians Society, who were happy with the concept and provided me with a list of their members. The list in those days was very short (unlike today), and I tried to fathom out who was a paediatrician or treated paediatric cases and added them to the mailing list.

The first few cases hardly garnered a response. I suspect people were too shy to answer. After a few weeks I would send out an expert opinion. The cases were all real cases (mostly from my own practice), and all had excellent lessons to teach. Gradually, as knowledge and familiarity with PDG grew, so the number of responses increased. Currently it's not unusual to have over 100 responses to a case.

The cases have spanned the whole range of paediatric HIV issues including opportunistic infections, side-effects of ART and ethical issues. At the moment we are concluding PDG No. 51.

Some notable cases include:

- One of the earliest cases in South Africa of Cushing's syndrome caused by an interaction between ritonavir and inhaled fluticasone for asthma.
- A child from a neighbouring country who was diagnosed as HIV-positive on two different tests and turned out to be HIV negative.
- An HIV-positive child with marked failure to thrive and a normal CD4 count who turned out to have an oesophageal stricture and is now thriving after oesophageal dilatation.
- Cases of lymphoma and Kaposi's sarcoma.
- A case where a mother with end-stage HIV had a negative HIV ELISA test, having lost the ability to make antibodies due to her poor immunity.
- A case of a young infant treated with ART very early on who became HIV ELISA negative after losing her maternal antibodies. She did, however, remain PCR positive.
- Interestingly, PDG No. 47 in April 2008 again discussed a patient with disfiguring parotomegaly and a normal CD4 count. This time the opinion was overwhelmingly in favour of starting ART.

The response to the PDG has been phenomenal. The mailing list currently stands close to 1 500. Subscribers are predominantly from South Africa but also include Namibia, Zimbabwe, Botswana, Zambia, Angola, Malawi, Kenya, Rwanda and other countries. Subscribers are predominantly doctors but also include nurses, pharmacists, and counsellors.

There is no doubt that the PDG has succeeded because of the very active participation of our subscribers and our wonderful panel of local and overseas experts, all of whom deserve my heartfelt thanks. I have merely been the conduit between the two.

If you would like to subscribe to the PDG, please send an e-mail to leonlevin@54.co.za. I am also constantly on the lookout for new cases to discuss. They can be sent to the same e-mail address.

LEON LEVIN
Head, Paediatric programmes
Right to Care

OPINION

THE EMERGING NEED FOR ADOLESCENT-FOCUSED HIV CARE IN SOUTH AFRICA

H B Jaspan[1], *MD, PhD, FAAP*
R Li[2], *MPhil*
L Johnson[3], *PhD, AIA*
L-G Bekker[1], *MB ChB, PhD, FCP*
[1]*Desmond Tutu HIV Centre, Institute of Infectious Diseases and Molecular Medicine, University of Cape Town*
[2]*Centre for Social Science Research, University of Cape Town*
[3]*Centre for Actuarial Research, University of Cape Town*

Before the widespread introduction of antiretroviral therapy (ART), most perinatally infected children did not survive beyond the first 2 years of life.[1] With treatment, HIV-positive children are living longer. In the developed world, where HAART has been widely available since 1996, survival of perinatally infected children into adolescence is now the norm. Of a French cohort of perinatally infected children born before 1993, 58% were still alive and receiving HIV care 13 years later.[2] In the UK the proportion of HIV-infected children in care aged 10 - 19 years increased from 11% to 44% between 1996 and 2005.[3] As HAART becomes increasingly available in South Africa, we can expect similar trends.

In addition to a growing population of vertically infected adolescents in South Africa, youth are among those at greatest risk of HIV acquisition.[4] Uptake of voluntary counselling and testing is low in adolescents, with only 20% of youth ever having had an HIV test[5] and even fewer engaging with the health care system for CD4 monitoring and health maintenance. At youth centres in the Cape Metropole, catering to 15 - 25-year-olds only, testing uptake is 85% and two-thirds go on to receive CD4 counts (Karen Jennings, personal communication). Although most horizontally infected adolescents are not in immediate need of treatment, they could benefit from care and certainly from knowledge of their HIV status.

Mathematical models can be used to project the growth in the numbers of adolescents needing antiretroviral treatment in South Africa. The ASSA2003 AIDS and Demographic model,[6,7] updated to reflect recent data on prevention of mother-to-child transmission[8] and paediatric survival on antiretroviral treatment,[9] estimates that by the middle of 2008, approximately 6 000 youth aged 10 - 19 were receiving highly active antiretroviral therapy (HAART) and a further 6 000 met entry criteria for HAART. If it is assumed that South Africa meets the National Strategic Plan target of providing antiretroviral treatment to 80% of all individuals progressing to AIDS,[10] the number of adolescents receiving antiretroviral treatment can be expected to increase to 153 000 by 2020. While youth aged 10 - 19 accounted for only 1% of the total number of patients receiving HAART in 2008, this proportion is expected to grow to approximately 5% by 2020, mainly as a result of vertically infected children surviving into adolescence. Treatment and care for HIV-positive adolescents will therefore become increasingly important over the next decade. This contrasts with other chronic childhood illnesses such as rheumatic heart disease, where the prevalence is declining. For example an estimated 46 cases of acute rheumatic fever were reported in 2002 in adolescents aged 10 - 19 years, only some of whom went on to develop rheumatic heart disease.[11]

Adolescent health care is distinct from both paediatric and adult heath care because of the physiological and psychosocial transitions that occur during this period. HIV interferes with these normal developmental processes by delaying physical and intellectual development. In addition, HIV-positive adolescents confront many extra challenges, including concerns about medication regimens, doctors' appointments, life expectancy, social upheaval, disclosure, stigmatisation, transmission of virus to others and the fear of being 'abnormal'. The combination of HIV-related issues that are common to any age group and the extensive and rapid changes of adolescence create an exceptional and formidable challenge for both young people themselves and the adults who care for them.

Providing quality care and treatment for HIV-positive adolescents requires distinct needs to be addressed:

- Young people living with HIV require knowledge and understanding of their HIV status. Disclosure of status at this age is paramount, although often not easy to accomplish. Once aware of their serostatus, adolescents require frank ongoing communication and education to ensure understanding of the implications and acceptance of living with their illness. While often deferred in childhood, disclosure is

crucial during adolescence as individuals approach cognitive maturity.[12] Significant adults may need to be guided and supported in this process.

- HIV places multiple stressors on the life of the adolescent, including side-effects from medication, chronic illness, real or perceived stigma, and frequently the death of family members. Young people living with HIV may struggle to achieve mental health. North American research has described high rates of mental disorders among HIV-infected adolescents, although it remains unclear whether these problems are associated with the virus itself or other environmental factors.[13] Whatever the cause, evidence suggests that young people living with HIV need appropriate psychological services for adjustment and survival of the youth into adulthood. This is particularly important given that mental health status affects HAART adherence and engagement in risky sexual behaviour.[14,15]
- Adolescents need social, emotional, spiritual, and often material support.[16] Often HIV-infected adolescents are alienated from their peers.[17] Support groups can provide this support where peers do not. However, such groups cannot replace support for daily living, where additional assistance is often required.
- Because adherence to treatment and treatment programmes is integral for sustaining positive health outcomes, HIV-positive young people need support in managing their treatment. During childhood, caregivers are often heavily involved in their children's daily routines, and provide instrumental help in taking tablets. However, as children grow up, expectations for them to take increasing responsibility for their medication and clinic appointments emerge. Among adolescents adherence is a major problem, and studies suggest that compliance during this period is lower than in other stages of life.[18-20] This is probably due to disease denial,[21] peer pressure and social norms, rebelliousness and risk-taking behaviour, among other reasons. In a local large, private sector, sub-Saharan African programme, where adolescents were treated similarly to adults, the adolescent patients were 1.5 times less likely to be virologically suppressed at one year, due to poorer adherence.[20] Adolescents therefore need targeted interventions that enhance adherence and promote responsible treatment management.
- Finally, young people living with HIV need to learn how to make healthy decisions about reproductive and sexual health. Like their HIV-negative peers, HIV-positive adolescents will be maturing sexually and will have questions about their ability to date and engage in sexual activity.[23,24] With sexual behaviour comes the potential for unwanted pregnancy, acquisition of other sexually transmitted infections, re-infection with more pathogenic virus, and transmission of the virus to others. The potential costs of unsafe sex are therefore exceptionally high for infected young people and their partners. Young people need age-specific sexual and reproductive health services, and information and counselling to minimise risky sexual behaviour and encourage positive sexual identities.[24]

We are currently in a critical moment of transition, during which the first generation of perinatally infected South African children are navigating their way through adolescence. As numbers increase, we need to plan for their distinct needs. Multidisciplinary adolescent-specific programmes, addressing both the biomedical and the psychosocial aspects of living with HIV, would help prevent young people from falling through the cracks of paediatric or adult-orientated health care services. A few such interventions, such as the National Adolescent Friendly Clinic Initiative, have already been implemented in a number of clinics and hospitals around the country[25] and should be monitored, evaluated, and expanded.

Adolescent-targeted care is a glaring gap in our health care system, where we have neither specialists nor wards to cater for teenagers with chronic illness. Endocrinologists, cardiologists, oncologists, and other specialities that care for adolescents in South Africa have been struggling with this challenge for years.[26,27] The HIV epidemic, with its unprecedented numbers and characteristic disease burden in youth, may provide the impetus for the South African medical system to address the specific needs of our adolescent population. Failing to do so may jeopardise the longevity of more than 150 000 adolescents requiring HAART in the next decade.

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OPINION

CALL TO ACTION: PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV

Ashraf Hassen Coovadia, *FCPPaed (SA), DCH (SA), Dip HIV Man (SA)*
Department of Paediatrics and Child Health, Rahima Moosa Mother and Child Hospital and University of the Witwatersrand, Johannesburg
Ameena Ebrahim Goga, *FCPPaed (SA), MSc, MCH, MSc (Epidemiol)*
Health Systems Research Unit, Medical Research Council, and Department of Paediatrics and Child Health, University of Limpopo, Medunsa campus, Ga-Rankuwa, Pretoria
Laurie Schowalter, *MPH*
Policy and Implementation, South African HIV Clinicians Society

The prevention of mother-to-child transmission of HIV (PMTCT) programme is a critical intervention to reduce the incidence of paediatric HIV infections. It is also a key intervention to decrease infant, child and maternal mortality. The optimal implementation of a sound, evidence-based PMTCT programme is essential to meet both the HIV reduction targets in the National Strategic Plan and to achieve Millennium Development Goals (MDGs) 4 (reducing infant and child mortality) and 5 (reducing maternal mortality). Since 2001, South Africa has been implementing a programme to prevent mother-to-child transmission (MTCT) of HIV. Since 2007, national PMTCT policy has evolved into a strong, enabling framework that should reduce vertical transmission significantly. This paper reviews the milestone studies that have contributed to our knowledge about drug regimens to reduce MTCT, and reviews the latest South African PMTCT guidelines and the possible future changes. Strengthened/revised drug regimens for PMTCT are essential but insufficient for measureable decreases in HIV transmission and improvements in maternal and child health. The main challenge is implementation. Until the enhanced PMTCT policy is effectively operationalised, measurable achievements will remain elusive.

Prevention of mother-to-child transmission of HIV (PMTCT) is the single most effective medical intervention to significantly reduce the burden of HIV in communities, and its optimal implementation is essential to meet both the HIV reduction targets in the National Strategic Plan (NSP)[1] and to achieve Millennium Development Goals (MDGs) 4 (reducing infant and child mortality) and 5 (reducing maternal mortality).[2] In 1994 the landmark Paediatric AIDS Clinical Trial Group (PACTG) 076 study found a 67% reduction in HIV transmission when pregnant women were given zidovudine (AZT) from the second trimester onwards and when infants received AZT for the first 6 weeks of life.[3] By demonstrating that vertical transmission was preventable, these data represented the most dramatic results in HIV research at the time. Global inequities were also highlighted, as the PACT 076 PMTCT interventions were not feasible in resource-limited settings. PACTG 076 was quickly followed by studies from Thailand[4] and Africa (Petra)[5] demonstrating that shorter courses of therapy were also highly effective, but these were still not feasible for large-scale implementation in most resource-limited settings. However, Thailand did implement the short-course therapy in 1999 as part of its national PMTCT policy. In 1999 the Ugandan HIVNET 012 study, conducted in a breastfeeding population, found that just a single dose of nevirapine (NVP) to the mother and a single dose to the child could reduce HIV transmission to 13%,[6] making PMTCT now accessible in resource-limited settings. Countries all over the world quickly implemented the PACTG and HIVNET 012 PMTCT regimens; in the USA, for example, transmission rates dropped sharply once guidelines for the use of AZT were adopted. Over a period of 6 years transmission rates in the USA dropped sharply and remain below 2% today largely as a result of HAART (highly active antiretroviral therapy) to mothers.[7] Over the decade after PACTG 076, evidence of the superiority of HAART or multidrug therapy to prevent mother-to-child transmission (MTCT) accumulated. In 2004, the Thailand PHPT-2 study found that the use of AZT combined with NVP ('dual therapy') could reduce HIV transmission to 1.9%,[8] forming the basis of the current South African PMTCT policy.

Since 1999 and the initial drug trials much work has been done to minimise, and possibly eliminate, vertical transmission of HIV. The World Health Organization (WHO) developed a comprehensive strategic four-pronged approach, based on providing a continuum of appropriate care for mothers and their infants, to prevent HIV infection in infants and young children and optimise maternal and child health. The four-prong strategy includes: (*i*) primary prevention of HIV infection; (*ii*) prevention of unintended pregnancies among HIV-infected women; (*iii*) prevention of HIV transmis-

sion from mother to child; and (*iv*) provision of care and support for HIV-infected mothers and their infants, partners and families.[9] This comprehensive strategy states that because primary HIV infection during pregnancy and breastfeeding poses an increased threat of MTCT, HIV prevention efforts should address the needs of pregnant and lactating women, especially in high-prevalence areas. The third prong (PMTCT) comprises five interventions, namely: (*i*) increasing access to HIV testing and counselling; (*ii*) provision of antiretroviral (ARV) therapy, the choice depending on local feasibility, efficacy and cost; (*iii*) implementation of safe delivery practices, including avoiding invasive obstetric procedures such as artificial rupture of membranes, fetal scalp monitoring and episiotomy; and (*iv*) providing optimal counselling and support on infant-feeding methods and provision of care and support, through all health programmes, for HIV-infected mothers, their infants, partners and families. This paper focuses mainly on the third prong, but acknowledges the importance of the other strategies.

THE DEVELOPMENT OF SOUTH AFRICAN POLICY ON PMTCT, AND EXPERIENCES THEREOF

In South Africa, the use of a single dose of NVP (at the onset of labour for mother, and within 72 hours for the baby) to prevent MTCT of HIV was implemented in 2001. Although the policy was in place, significant implementation obstacles remained. At the inception of the programme there was insufficient guidance on *how* to implement PMTCT, resulting in inconsistent programme implementation across the country, and in PMTCT being mainly a vertical programme that was implemented independently of maternal, neonatal and child health services. The science also continued to advance.

As the evidence continued to mount on the superiority of multidrug therapy, academics, clinicians and civil society in South Africa mobilised and advocated for the urgent adoption of an updated PMTCT policy incorporating dual therapy, particularly in the wake of updated WHO PMTCT guidelines in 2006.[9] In early 2008 the National Department of Health (NDoH) updated the PMTCT guidelines.[10] Changes included: (*i*) a slight change in the testing strategy, calling this a *routine offer of voluntary counselling and testing;* (*ii*) the addition of AZT from 28 weeks of gestation and a renewed emphasis on getting CD4 counts on all pregnant women to determine the need for initiation of highly active antiretroviral therapy (HAART) in pregnancy (CD4 cell count <200 cells/µl or WHO clinical stage 4); and (*iii*) improved guidance on infant feeding options and a greater emphasis on ensuring infant diagnosis at 6 weeks of life. These guidelines are undergoing further review at the time of writing, with recommendations from the PMTCT guidelines committee to lower the threshold for the initiation of HAART in pregnancy, starting with a CD4 count of 350 cells/ µl or less. This significant change, coupled with the new proposed paediatric guidelines (NDoH 2009) calling for the early treatment of all HIV-infected infants regardless of CD4 count, creates the necessary policy framework to set South Africa on a path to achieving both MDGs 4 and 5 and the HIV reduction targets set in the NSP 2007 - 2011.

CURRENT STATE OF THE NATIONAL PMTCT PROGRAMME

While a sound PMTCT policy is a significant step in the right direction, in itself this is insufficient for programme success. Data show that implementation of the national PMTCT programme has been fraught with challenges since its inception:[11] among other issues, these relate to lack of health system capacity to absorb the programme into routine care, lack of health worker knowledge about PMTCT, confusing messages about PMTCT and infant feeding, and PMTCT messages that do not fit into current socio-cultural frames of reference. Consequently all of the available evidence on HIV seroprevalence and maternal and child mortality indicate that South Africa is well behind in meeting its NSP and MDG targets, and is therefore unlikely to achieve these without a major improvement in the performance of its HIV programmes.

Data from several PMTCT-related studies show that early vertical transmission rates vary from 7% to 19%,[12-14] that 9-month HIV-free survival might range between 64% and 80%,[15] and that guidelines on infant feeding and especially breastfeeding cessation were not feasible and not adhered to,[16] despite the implementation of PMTCT interventions. National data on the effectiveness and impact of the PMTCT programme are still unavailable. In the first half of 2009, approximately 40% of HIV-exposed infants accessed an HIV polymerase chain reaction (PCR) test before 3 months of age nationally compared with approximately 32% over the same time period in 2008 (unpublished data). While it is encouraging that the average prevalence of positivity among those tested declined from 10% in 2008 to 7% in 2009, there is no measure of the rate of paediatric HIV infection in the more than half of HIV-exposed infants in the country whose mothers are less likely to be accessing PMTCT services.

Furthermore, data from the just-released 2008 National Antenatal Sentinel HIV and Syphilis Prevalence Survey found that HIV infection among antenatal clinic attendees is at an unacceptably high level of 29.3%.[17] This figure is a national aggregate, with a range of seroprevalences across provinces and even more vari-

ation across the 52 districts. The distribution of HIV prevalence by district in 2008 ranged from 2.2% in the district of Namakwa (Northern Cape) to 45.7% in uMgungundlovu (KwaZulu-Natal), the highest recorded in the country. An investigation into these differences as well as the coverage and quality of PMTCT services across all districts would be instructive in designing implementation strategies.

The District Health Barometer (DHB), an annual assessment of performance on key health indicators in the public health sector conducted by the Health Systems Trust, corroborated evidence of suboptimal PMTCT programme implementation based on the District Health Information System (DHIS).[18] The DHB has published data since 2005, so improvements over time can be measured. The 2007/2008 report found that the national antenatal HIV testing average increased from 69% in 2006 to 80% in 2007/2008. While this indicates an improvement in testing rates, the numbers are well short of the NSP 2009 target of 90%. The report also found huge variations in the uptake of NVP by pregnant women, ranging from 12% to 108%, with a national average of 76% – an increase on the 61% from the year before. While there are significant weaknesses with this data set, the trend and overall data set across all districts provide useful insights into the level of coverage and quality of the programme nationally.

A review of three South African mortality audit reports (*Saving Mothers – 2004, Saving Babies* and *Saving Children*) called the 'Every Death Counts' report found South Africa in the unenviable position of being a country where maternal and child mortality has *increased* since the baseline for the MDGs in 1990.[19] In that report, citing the *Saving Mothers* report of 2004, the largest cause of maternal mortality was reported to be non-pregnancy related, with infections such as HIV, tuberculosis and pneumonia accounting for the deaths of approximately 38% of the women.[19] Similarly, HIV/AIDS accounted for 35% of premature deaths among neonates and children.[19] The latest *Saving Mothers* report (2005 - 2007) sadly shows the same trend as earlier, with about 44% of maternal deaths caused by non-pregnancy-related infections (mostly AIDS).[20] The time to consider a paradigm shift from narrowly thinking of PMTCT as simply an intervention of reducing vertical transmission of HIV to seeing this programme as key for the survival of women, children and indeed families is long overdue.

The available data indicate that a sound PMTCT policy is insufficient to assure HIV transmission rates of less than 5%. South Africa now faces a more mundane struggle in the battle against HIV: the battle of implementation.

CHALLENGES AND OPPORTUNITIES

There are numerous and varied implementation challenges faced by the programme at several levels. The interruption of essential drugs, scarce human resources at sites, HIV stigma and discrimination, and lack of clear operational guidelines at provincial and local levels remain serious hurdles to achieving smooth implementation of the programme and optimisation of maternal and child health outcomes. A culture of accountability for optimisation of the programme and attainment of targets is required at all levels of health care providers as well as by health care managers from facility level up to the NDoH.

Under the current system, there are few incentives for health care personnel to ensure that the PMTCT programme is performing optimally. For instance, no health manager's annual performance appraisal takes PMTCT performance targets into account, and health care facilities are not routinely audited on PMTCT outcomes with a view to assigning responsibility for improved performance. In order to strengthen the focus of health care facilities and ensure management support and rigorous stewardship, the NDoH should not only request accurate reports on PMTCT indicators (e.g. percentage of mothers tested for HIV) on a regular basis, but also include the site's PMTCT programme performance in every relevant manager's portfolio of performance assessment. Programme data collected at a site are rarely used for ongoing feedback to staff on their own performance, or as a tool for quality improvement. Health care facilities and provincial and district departments of health must make use of data to monitor PMTCT performance and assist all sites in meeting national goals.

Health care facilities must also re-invigorate their HIV counselling and testing programme to ensure that all women entering antenatal clinics are offered an HIV test and all infants attending well-baby/immunisation clinics are assessed for HIV exposure. There is a move within the NDoH towards provider-initiated counselling and testing, placing a greater emphasis on health care providers to ensure they discharge their duty to present HIV testing as a routine procedure with life-saving benefits. Given that approximately 3% of women who initially test negative will seroconvert during pregnancy,[22] systems must also be in place to retest HIV-negative women at around 34 weeks of gestation and in the immediate postnatal period before mother and baby are discharged. Health care workers bear a responsibility to both mothers and children to ensure that no woman leaves a health care facility unaware of her HIV status. Failure to do so would be tantamount to negligence, given the availability of life-saving and

life-prolonging therapy, not to mention the option of preventing a paediatric HIV infection. Retesting should also be strongly encouraged at later points in the postnatal period when the mother is seen as part of her follow-up care.

PMTCT targets can only be achieved by deliberately addressing the challenges and weaknesses in the system. All health care personnel in the facility must be educated on the importance of PMTCT and of the integral role the programme plays in infant, child and maternal survival. A designated team with an identified leader must take responsibility for PMTCT programme performance. Until there is a renewed emphasis on responsibility for the PMTCT programme within each health care facility, a lack of programme ownership will continue to prevail.

While the challenges may seem vast, there are a number of outstanding solutions that have been applied to overcome key bottlenecks and challenges in PMTCT implementation in South Africa from which much can be learned. The NDoH, Medical Research Council, University of the Western Cape and UNICEF jointly developed a 'Possible solutions' document that highlighted these.[21] The document highlights districts or facilities that have applied a comprehensive or selective approach to overcoming key bottlenecks in PMTCT. Of note is the success that facilities have experienced when they integrate PMTCT care into routine care, e.g. when the birth register was adapted to include PMTCT information, when community-based activities to increase the demand for PMTCT services were implemented, or when data were used at a local level to monitor and improve PMTCT-related care. This 'Possible solutions' document highlights that progress can be achieved when health care facilities apply ingenuity, creativity and commitment to improving PMTCT programmes.

CONCLUSION

PMTCT has been implemented in South Africa since 2001, first in 18 pilot sites and now nationally in more than 3 000 facilities. Despite the limited documented impact of the programme (and there is a dearth of data in this regard), PMTCT has now received support for renewed action at the highest political level. The current Minister of Health (Hon. Aaron Motsoaledi) has been frank in his admission that 'South Africa is losing the battle against HIV and that maternal deaths are at unacceptably high levels'. His administration has renewed its commitment to the programme and has announced an accelerated PMTCT programme aimed at improving its coverage and quality. The NDoH is currently revising the PMTCT policy, which it is hoped will initiate HAART in all pregnant women with a CD4 count <350 cells/µl and in all HIV-infected infants less than 12 months old. These policy changes will help set South Africa on a path towards achieving HIV reduction targets and improved child and maternal health. The government is demonstrating leadership and political will. As health care workers we must recommit to the PMTCT programme, bring a shared sense of responsibility and accountability for improving maternal, newborn and infant health, and move beyond policies so that they become sustained action at all levels of the health care system. It is only when this occurs that we will meet the targets set in the NSP and meet the 4th and 5th MDGs.

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ORIGINAL ARTICLE

A WINDOW INTO A PUBLIC PROGRAMME FOR PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV: EVIDENCE FROM A PROSPECTIVE CLINICAL TRIAL

M Cotton[1], *FCPaed (SA), PhD*
S Kim[2], *ScD (Biostats)*
H Rabie[1], *FCPaed (SA)*
J Coetzee[1], *CPN, PN*
S Nachman[3], *MD for the PACTG 1041 team*
[1]*Centre for Infectious Diseases, Department of Paediatrics and Child Health and KID-CRU, Tygerberg Children's Hospital and Faculty of Health Sciences, Stellenbosch University, Tygerberg, W Cape*
[2]*Department of Biostatistics, Harvard School of Public Health, Boston, Mass, USA*
[3]*Division of Infectious Diseases, State University of New York, NY, USA*

Objectives. To evaluate efficacy of the antenatal, intrapartum and postnatal antiretroviral components of a public service prevention of mother-to-child (PMTCT) programme in infants.

Design. Analysis of prospectively collected screening data of demographic and MTCT-related interventions and HIV infection status of infants identified through HIV-specific DNA polymerase chain reaction.

Setting. Tygerberg Children's Hospital, Western Cape, South Africa.

Subjects. HIV-infected women and their infants identified through participation in a public service PMTCT programme were referred for possible participation in a prospective study of isoniazid prophylaxis.

Interventions. Key components of the programme include voluntary counselling and testing, administration of zidovudine to the mother from between 28 and 34 weeks' gestation and to the newborn infant for the first week, single-dose nevirapine to the mother in labour and to the newborn shortly after birth, and free formula for 6 months.

Main outcome measures. Number and percentage of HIV-infected infants and extent of exposure to antenatal, intrapartum and postnatal antiretrovirals.

Results. Of 656 infants with a median age of 12.6 weeks, screened between 1 April 2005 through May 2006, 39 were HIV-infected, giving a transmission rate of 5.9% (95% confidence interval (CI) 4.4 - 8.0%). Antenatal prophylaxis was significantly associated with reduced transmission (odds ratio (OR) 0.43 (95% CI 0.21 - 0.94)) as opposed to intrapartum and postpartum components (p=0.85 and p=0.84, respectively). In multivariable analysis the antenatal component remained significant (OR=0.40 (95% CI 0.19 - 0.90)).

Conclusions. The antenatal phase is the most important antiretroviral component of the PMTCT programme, allowing most opportunity for intervention.

HIV infection has a high prevalence in antenatal attendees in South Africa. In the annual seroprevalence survey conducted through the National Department of Health from 2005, the prevalence in the Western Cape province was 15.7%.[1] Here, a pilot zidovudine (ZDV)-based prevention of mother-to-child transmission (PMTCT) programme began in 1999,[2] and has gradually been expanded since January 2001. Since April 2003 the PMTCT interventions have been available at all public sector antenatal service facilities in the province (300 antenatal clinics and 53 delivery centres and hospitals) and 350 primary health care clinics where infant follow-up occurs. Attendees are offered voluntary, confidential counselling and testing (VCT) and if HIV positive, antiretrovirals (ARVs) for the mother and infant. Uptake was reported as 97% in 2006 (Status Report – Prevention of Mother-to-Child Transmission Programme, 14 July 2006, HIV/AIDS/STI Directorate,

Western Cape). Follow-up of mother and infant, co-trimoxazole from 6 weeks of age and modified infant feeding practices are also important components. The majority of women (95%) choose formula feeding, which is provided free for the first 6 months.

The initial ARV intervention was single-dose nevirapine (sd-NVP) to mother and infant, introduced after the success of the HIVNET 012 study.[3] Since mid-2003, ZDV was added from 34 weeks' gestation for the mother and for a week for the neonate.[4] In early 2006, antenatal ZDV from 28 weeks was gradually introduced. With the advent of the national antiretroviral rollout in 2004, all pregnant women with a CD4 count below 200 cells/µl were offered highly active antiretroviral therapy (HAART).

PACTG 1041 is a prospective phase III clinical trial evaluating the efficacy of isoniazid (INH) primary prophylaxis in HIV-exposed infected and uninfected infants. Through screening for this trial at Tygerberg Children's Hospital (TCH), we had the opportunity to evaluate the PMTCT programme in referred infants.

METHODS

HIV-exposed infants between 3 and 4 months of age were referred for study participation from health care facilities in the urban and semi-rural areas close to TCH. Referring clinics were requested not to refer infants exposed to TB. Infants were pre-screened by lay counsellors and nurses for eligibility to enrol in PACTG 1041. Exclusion criteria included exposure to tuberculosis and not receiving bacille Calmette-Guérin (BCG) immunisation within the first week of life. Eligible subjects were entered onto a screening log, comprising the dataset for the present report.

A medical doctor undertook formal screening. Note was taken of the extent of participation in the PMTCT programme and whether the mother received HAART in pregnancy.

Those receiving either antenatal HAART or ZDV were categorised as having received antenatal prophylaxis. Intrapartum prophylaxis was either ZDV or NVP or both. Postnatal intervention to the neonate was either ZDV or NVP or both.

HIV DNA polymerase chain reaction (PCR) was performed on all exposed infants eligible for the trial. All samples were tested in duplicate. For discordant results, the test was repeated in duplicate.

Simple percentages were used to estimate rates of transmission and 95% confidence intervals (CIs) were based on the score method. Medians and interquartile ranges (IQR) were used to summarise continuous data. Logistic regression was used to evaluate the effectiveness of PMTCT components. Odds ratios (ORs) were calculated through the logistic regression model and 95% CIs are based on the profile likelihood. For antenatal HAART, Fisher's exact test was used because of the small cell size. In multivariable logistic regression analysis, we evaluated all two-way and three-way interactions between the three PMTCT programme components and found no statistically significant interactions, and therefore present a multivariable model that includes main effects for the three components. All tests are two-sided at the 5% significance level and are not adjusted for multiple comparisons. Analyses were done using SAS 9.1 (Cary, NC, USA).

Permission to conduct P1041 and to report on antenatal interventions was obtained from the Committee for Pharmaceutical Trials, Stellenbosch University, and the Medicines Control Council of South Africa. The trial was approved by the National Institute of Allergy and Infectious Diseases (NIAID) according to the Office of Human Rights Protection, National Institutes of Health guidelines.

RESULTS

Between 1 April 2005 and 31 May 2006, 773 infants were referred for pre-screening. Seven infants were excluded because their mothers were HIV-negative and had been referred in error. One hundred and ten HIV-exposed infants were excluded at pre-screening, of whom 52 (47.3%) had known exposure to tuberculosis.[5] Other common reasons included the infant being too old for participation in the INH trial (15), BCG given after 7 days of life (15) and family relocating (7).

Six hundred and fifty-six infants were entered onto the screening log and are reported on here. The median age (IQR) of infants was 12.6 (11.0 - 13.6) weeks and that of mothers 26 (23 - 30) years. Thirty-nine of 656 infants had a positive HIV DNA PCR, giving a transmission rate of 5.9% (95% CI 4.4 - 8.0%). Two hundred and seventy-eight (85.8%) of 324 mothers who were asked decided on exclusive formula feeding.

Data on transmission and extent of participation in the PMTCT programme are shown in Table I. We evaluated the antenatal, intrapartum and postnatal components of the programme separately, using logistic regression (Table II). We found that antenatal prophylaxis was significantly associated with a reduction in rate of transmission (OR 0.43 (95% CI 0.21 - 0.94), p=0.035) as opposed to intrapartum and postnatal components (p=0.85 and p=0.84, respectively).

The results of fitting a multivariable logistic regression model to the data, which included the three components of the PMTCT programme, are shown in Table III.

TABLE I. EXTENT OF PARTICIPATION OF MOTHERS AND THEIR INFANTS IN THE PMTCT PROGRAMME AND HIV TRANSMISSION RATES

PMTCT	Screened (*N* (%))* 656	Infants HIV-infected (*N* (% of screened)) 39 (5.9)
Full participation	348 (53.0)	21 (6.0)
Antenatal only	105 (16.0)	4 (3.8)
Antenatal + postnatal (no intrapartum)	42 (6.4)	1 (2.4)
Antenatal + intrapartum	15 (2.3)	1 (6.7)
Postnatal only	39 (5.9)	4 (10.3)
Intrapartum only	18 (2.7)	1 (5.6)
Intrapartum + postnatal	25 (3.8)	3 (12.0)
None	13 (2.0)	3 (23.1)
No data	51 (7.8)	1 (2.0)

*Percentages do not add to 100.0 due to rounding.
Antenatal = either ZDV or HAART; intrapartum and postnatal = sd-NVP, ZDV.

TABLE II. UNIVARIATE ANALYSES

Programme component	Received component/total (%) Infant not HIV infected	Infant HIV infected	OR (95% CI)	*p*-value†
Antenatal PMTCT	483/568 (85.0)	27/38 (71.1)	0.43 (0.21 - 0.94)	0.035
Intrapartum PMTCT	380/568 (66.9)	26/38 (68.4)	1.07 (0.54 - 2.25)	0.85
Postnatal PMTCT	425/568 (74.8)	29/38 (76.3)	1.08 (0.52 - 2.48)	0.84
Antenatal HAART*	56/564 (9.9)	1/38 (2.6)	0.25 (0.01 - 1.52)	0.24

*Exact CI and Fisher's exact test *p*-value provided for antenatal HAART due to the small number of infections among those who received antenatal HAART.
†Likelihood ratio test from logistic regression model, except for antenatal HAART which is a Fisher's exact test.

TABLE III. MULTIVARIABLE ANALYSIS

PMTCT component	Adjusted OR (95% CI)	*p*-value*
Antenatal	0.40 (0.19 - 0.90)	0.027
Intrapartum	1.26 (0.57 - 2.89)	0.57
Postnatal	1.05 (0.46 - 2.60)	0.91

*Likelihood ratio test.

The antenatal component of the PMTCT regimen remained significant in the multivariable model, indicating that it is an independent predictor of decreased transmission (OR 0.40 (95% CI 0.19 - 0.90), *p*=0.027).

Of 57 mothers with CD4 cell counts below 200/µl receiving HAART, only 1 (1.8% (95% CI 0.3 - 9.3%)) transmitted HIV to her infant versus 26 of 453 with CD4 counts >200/µl not receiving HAART (5.7% (95% CI 3.9 - 8.3%), *p*=0.34).

Fifty-one (7.8%) mother/infant pairs with missing PMTCT information were excluded from the above analyses. Of these, only 1 woman (2.0% (95% CI 3.5 - 10.3%)) transmitted HIV to her infant.

DISCUSSION

There is little information on vertical transmission in the absence of intervention in South Africa. Transmission rates vary between 15% and 34%.[6,7] In the ZDV-based pilot programme in Khayelitsha, Western Cape, the transmission rate was 11%.[2] In a study evaluating sd-NVP in different South African settings, the transmission rate in Paarl, a recruitment site for P1041, was 8.3% at 3 weeks of age.[8] The combination of antenatal ZDV from 28 weeks and sd-NVP under optimal circumstances is associated with a transmission rate as low as 1.1%.[4]

Our data confirm a relatively effective PMTCT programme despite only 53% actually participating in all components of the programme. Importantly, an additional 25% received antenatal ARVs. A multi-faceted intervention programme means that there are many opportunities for intervention, as opposed to one relying on only a single intervention such as sd-NVP, which, if missed, severely compromises efficacy. The World Health Organization has endorsed the programme as practised in the Western Cape.[9] Our data confirm the relative importance of antenatal as opposed to perinatal or postnatal intervention. The transmission rate of 5.9% was achieved due to concerted efforts to facilitate success of the programme despite widespread perceived obstacles to initial implementation.[10] Although we did not record duration of antenatal ARVs in each case, 75% of mothers were reported to have received ≥2 weeks of therapy, defined as adequate by the programme (personal communication – Pauline Pieters, PMTCT Co-ordinator, 20 September 2006).

An important preliminary finding in our study is that among women with CD4 cell counts <200/µl, only 1 of 57 mothers on HAART (1.8%) transmitted HIV, as opposed to 26 (5.7%) of 453 mothers receiving ZDV. Although this was not statistically significant, we expect-

ed more transmission among these mothers because of their low CD4 counts before initiation of HAART.

There are a number of limitations to our study. We did not record the mothers' CD4 counts; rather, we assumed that they were appropriately managed according to the PMTCT guidelines. Also, we only screened infants whose mothers expressed interest in their infants participating in the INH study. Nevertheless, our data are similar to those of the Department of Health, Western Cape, which reports a transmission rate of 6.2% (personal communication – Pauline Pieters, PMTCT Coordinator, 20 September 2006).

There were missing PMTCT data on 7.8% of screened mother/infant pairs, and the transmission rate was low in this group (2.0%). If we assume that none of these women received any component of PMTCT or that these women received all components of PMTCT, the conclusions drawn here remain unchanged.

The antenatal ARV component is extremely important for reduction of MTCT and reduces intra-uterine infection, For example, Lallemant *et al.* showed that initiating ZDV at 28 weeks was far more effective than at 35 weeks and was not compensated for by extending postnatal ZDV for 6 weeks.[11] Nevertheless, the intrapartum and postnatal components also have an important role. For example, Wade *et al.* showed that in the absence of ZDV, perinatal transmission of HIV was 26.6% (95% CI 21.1 - 32.7%).[12] When ZDV was begun antenatally, the transmission rate was 6.1% (95% CI 4.1 - 8.9%). Administration of postnatal ZDV alone within 48 hours of life had a transmission rate of 9.3% (95% CI 4.1 - 17.5%), indicating the importance of the postnatal component.[12] Gray *et al.* found postnatal sdNVP to be slightly more effective than ZDV for 6 weeks when neither antenatal nor intrapartum ARVs could be given.[13]

CONCLUSIONS

The public service PMTCT programme in the Western Cape has successfully reduced the vertical transmission of HIV. The antenatal ARV component is critical for success.

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REVIEW

INFANT FEEDING AND HIV

Towards a new policy and implementation plan for minimising postnatal HIV transmission and maximising infant HIV-free survival

Ameena Ebrahim Goga, *FCPaed, MSc MCH, MSc (Epidemiol)*
Health Systems Research Unit, Medical Research Council, and Department of Paediatrics and Child Health, University of Limpopo, Medunsa campus, Ga-Rankuwa, Pretoria

Recent studies on antiretroviral prophylaxis during breastfeeding show that maternal highly active antiretroviral therapy (HAART) (alone or with 1, 4 or 24 weeks' infant prophylaxis) or infant prophylaxis alone for 6, 14 or 24 weeks (with limited maternal prophylaxis) reduces HIV transmission through breastmilk (postnatal transmission). Maternal postnatal regimens appear to be as efficacious as infant postnatal regimens, although one study shows a trend favouring infant nevirapine over maternal HAART (both used from 1 week to 6 months after delivery). These new findings necessitate a review of existing interventions to prevent mother-to-child transmission of HIV (PMTCT) , and the immediate implementation of regimens that reduce postnatal transmission – where this is feasible – to save children's lives.

In the public sector, while stakeholders engage in discussions about which is the best regimen to minimise postnatal transmission, **SSSUPPORT** should be given to all HIV-positive women to improve infant outcomes and reduce postnatal transmission, as follows: **Screen** all women for HIV, **Send** off CD4 cell counts on all HIV-positive women, **Screen** all HIV-positive women for AFASS using a standardised tool (e.g. Table II/Fig. 2 below); **Understand** the woman's personal and socio-cultural context; **Promote** exclusive or predominant breastfeeding if all AFASS criteria are not met; **Promote** exclusive formula feeding if all AFASS criteria are met; **Organise** supplies of formula milk and co-trimoxazole; **Review** mothers and infants in the first 3 days after delivery, in the first 2 weeks postnatally, and monthly thereafter, and review health and feeding practices, regardless of feeding choice, at every visit; lastly **Treat** all pregnant women with HAART if they meet national criteria for HAART initiation.

In resource-limited settings, infant feeding is the weakest link in programmes to prevent mother-to-child transmission of HIV. Although new perinatal HIV infections have been almost eliminated in resource-rich settings, elimination of new paediatric infections remains elusive in resource-limited settings, where HIV transmission through breastmilk accounts for approximately 40% of new infections.[1] Over the past 5 years, rigorously designed research, using varied study designs, has increased our knowledge about HIV transmission through breastmilk almost exponentially. However, implementing these findings has lagged far behind. A review of data shows that challenges to implementing current policies on infant feeding and HIV can be categorised into four main areas: (*i*) health care provider confusion about infant feeding and the risks of HIV transmission through breastfeeding;[2,3] (*ii*) poor support for infant feeding counsellors – qualitative research from Tanzania revealed a high level of stress and frustration among nurse counsellors, who were confused about the appropriateness of infant feeding options in the context of HIV;[4] (*iii*) poor counselling skills[5,6] – in three South African sites, structured observations of 22 counsellors and exit interviews with 60 mothers attending prevention of mother-to-child transmission (PMTCT) clinics showed that only 2 of 34 (5.9%) HIV-positive mothers were asked about essential conditions for safe formula feeding during counselling on infant feeding options, and fewer than a quarter of mothers expressed confidence in implementing their feeding decisions;[6] and (*iv*) a disjunction between feeding recommendations and the socio-cultural context within which feeding occurs[4,7-11] – in South Africa exclusive feeding practices recommended by current guidelines are not practised unless intense support is provided,[10-12] and in Tanzania nurse counsellors perceived both exclusive breastfeeding (EBF) and exclusive formula feeding as culturally and socially unacceptable, and therefore expressed a lack of confidence in their ability to counsel about HIV and infant feeding.[4]

This paper aims to contribute to the debate on how postnatal HIV transmission can best be minimised,

and how current recommendations on HIV and infant feeding can be implemented, in a southern African context. The paper is divided into three sections: the first provides a historical overview of infant feeding in the context of HIV (for readers new to the field of infant feeding and HIV), summarises new research on postnatal prophylaxis, and discusses the implications thereof; the second section summarises existing international and national recommendations on HIV and infant feeding; and the third section focuses on how we can implement existing, and possibly new, feeding recommendations in the context of HIV.

HISTORICAL OVERVIEW OF INFANT FEEDING IN THE CONTEXT OF HIV, AND IMPLICATIONS OF RECENT FINDINGS

Table I summarises the key studies that have contributed towards the body of knowledge on HIV and infant feeding.

The recent groundbreaking studies on maternal or infant prophylaxis during breastfeeding (Table I)[13-19] yield data that should prompt immediate action and a review of existing guidelines on infant feeding and HIV. However, as highlighted by Mofenson,[20] the perfect regimen to minimise postnatal HIV transmission through breastmilk is still difficult to identify as studies have major differences. These include differences in antepartum antiretroviral drug administration and duration, the duration of prophylaxis during breastfeeding, maternal CD4 cell counts at study entry, and rates of EBF. Mofenson also points out that several studies do not specify breastfeeding duration, and hence the time at risk for postnatal HIV transmission, while others do not provide infant HIV status at birth, making it difficult to compare the incremental benefit of antiretroviral prophylaxis during breastfeeding.[20]

Despite these differences, the main message from recent studies on prophylaxis during breastfeeding is that maternal highly active antiretroviral therapy (HAART) alone[16] or with 1 week,[14] 4 weeks[18] or 24 weeks of infant prophylaxis,[13] or infant prophylaxis alone (with limited maternal prophylaxis – i.e. no HAART) for 6 weeks,[19] 14 weeks[17] or 24 weeks,[15] reduces postnatal HIV transmission (i.e. breastmilk transmission). Maternal postnatal regimens appear to be just as efficacious as infant postnatal regimens, although the Breastfeeding, Antiretroviral and Nutrition (BAN) study suggests that at 28 weeks there was a trend favouring infant nevirapine over maternal HAART (both used from 1 week to 6 months after delivery).[13] The Post Exposure Prophylaxis to the Infant (PEPI) study showed that, when risk factors were adjusted for (maternal CD4 cell count, maternal presentation, sex of infant and infant birth weight), 9-month HIV-free survival was higher among infants who received 14 weeks' postnatal prophylaxis compared with control infants who only received 1 week's antiretroviral (ARV) cover (Table I).[17] Both the PEPI and Six Week Extended Dose Nevirapine (SWEN) studies show that the protective effect of infant postnatal prophylactic ARV regimens on breastmilk HIV transmission stops once the regimens stop being taken.[17,19]

IMPLICATIONS OF RECENT FINDINGS

These messages suggest that any of the new regimens highlighted in Table I could be implemented without further delay among breastfeeding HIV-positive mothers to reduce transmission where the human resource, financial and socio-cultural capacity exists to do this, e.g. in private sector facilities, despite the inherent inequity in this approach. Even one new paediatric infection is one too many! The ideal regimen for a national public health policy still needs to be decided upon, and should be guided by data. The choice is between prophylactic maternal HAART antenatally and thoughout breastfeeding, similar to regimens used in Kesho Bora[14] or MITRA-Plus[16] (Table I), a modified BAN regimen (Table I) with maternal dual prophylaxis (modified BAN) with or without tail cover and infant nevirapine for 6 months,[13] or a modified SWEN[19] or PEPI[17] regimen, with better maternal prophylaxis and nevirapine for 6 - 14 weeks. For women who start HAART for their own health antenatally, there is currently little debate about the postnatal regimen as HAART will continue postnatally and will consequently cover the breastfeeding period if the mother breastfeeds.

For resource-limited public health settings or countries, including South Africa, that are seeking to minimise postnatal HIV transmission, three main issues need to be considered when deciding on which ARV regimen to include in a national policy: (*i*) the basic science: efficacy and possible effectiveness of various postnatal prophylactic regimens using HIV transmission and HIV-free survival as the main outcomes; (*ii*) the feasibility of each regimen from a user perspective, i.e. for pregnant women, for mothers who may need treatment after delivery, and for infants who may need treatment after delivery; and (*iii*) feasibility of each regimen from a health system/service perspective, including cost, cost-benefit, procurement, packaging and delivery systems. Work needs to be undertaken urgently to examine the issues raised above, so that appropriate, effective and feasible new regimens that minimise postnatal HIV transmission can be instituted in the public health system without further delay.

It is likely that the most appropriate policy for postnatal prophylaxis would be one that starts early, ensures that mothers who need HAART for their own health receive treatment early, ensures that the postnatal regimen would not compromise any subsequent treatment needed by mother or infant (by increasing resistance, thus decreasing maternal treatment options), is feasible from a health system and community perspective, and is cost-

TABLE I. KEY STUDIES THAT HAVE CONTRIBUTED TO THE BODY OF KNOWLEDGE ON HIV AND INFANT FEEDING

Year, author, setting, study design, and characteristics of population	Regimens		Results and major contribution
	Mother	Baby	
1997 Ekpini *et al.*[36] Abidjan POC All BF	None	None	HIV transmission rate till 6 months: 28% (19 - 39%) for children born to HIV-1-infected women and 18% (9 - 30%) for children born to HIV-2-infected women HIV transmission rates after 6 months for HIV-1- and HIV-2-infected women: 12% (3 - 23%) and 6% (0 - 14%), respectively, adjusting for loss to follow-up **Main messages: The risk of transmission continues throughout the BF period. Early cessation of BF at 6 months of age is a possible intervention to reduce postnatal HIV transmission**
1999 Miotti *et al.*[37] Malawi POC All BF	None	None	7% of the 672 infants became HIV infected while BF. No infant became HIV positive after BF had stopped. The cumulative risk of infection for infants continuing to BF after 1 month to the end of months 5, 11, 17, and 23 was 3.5%, 7%, 8.9% and 10.3%, respectively. However, HIV infection rates per person per month were 0.7% in months 1 - 5, 0.6% in months 6 - 11, 0.3% in months 12 - 17, and 0.2% in months 18 - 23 (p=0.01), suggesting that HIV transmission decreases significantly as the child gets older **Main messages: Breastmilk transmission continues throughout the BF period, but decreases as the child gets older, and stops when BF stops**
1999 Semba *et al.*[38] Blantyre, Malawi POC All BF	None	None	Mothers of HIV-infected infants have significantly greater breastmilk viral load than mothers of uninfected infants Mastitis – probably as a result of poor BF technique – and breastmilk viral load were independently associated with MTCT of HIV-1 at 6 months (OR 2.38, 95% CI 1.26 - 4.42, and OR 2.97, 95% CI 1.23 - 7.18, respectively) **Main messages: Higher breastmilk viral load increases transmission risk through breastmilk. Mastitis also increases risk of HIV transmission, independently of breastmilk viral load**
2001 Nduati *et al.*[39] Nairobi, Kenya RCT Women randomised to BF or FF (clean water available and formula subsidised)	None	None	The cumulative probability of HIV-1 infection at 23 months was 36.7% (95% CI 29.4 - 44%) in the BF arm and 20.5% (95% CI 14 - 27%) in the formula feeding arm, p=0.001 The estimated rate of transmission (excess risk of transmission) was 16.2% (95% CI 6.5 - 25.9%). 44% of HIV-1 infection was attributable to breastmilk Kaplan-Meier estimates of the 2-year mortality rate were similar in the BF arm (24.4% (95% CI 18.2 - 30.7%) and formula feeding arm (20.0% (95% CI 14.4 - 25.6%)), p=0.30. The 2-year HIV-free survival rate was significantly lower in the BF arm (58%) compared with the formula feeding arm (70%), p=0.02 **Main messages: Most breastmilk transmission seemed to occur early during BF; however, transmission risk difference continued to increase throughout the BF period. HIV-free survival at 2 years was better in the formula feeding arm**

TABLE I. KEY STUDIES THAT HAVE CONTRIBUTED TO THE BODY OF KNOWLEDGE ON HIV AND INFANT FEEDING (CONTINUED)

Year, author, setting, study design, and characteristics of population	Regimens		Results and major contribution
	Mother	Baby	
2001 Coutsoudis *et al.*[24] Cato Manor – urban area, South Africa Unexpected findings from a vitamin A RCT Women self-selected to EBF or EFF	None	None	Cumulative probabilities of HIV detection were similar among never and exclusive breastfeeders up to 6 months (0.19, 95% CI 0.14 - 0.26 and 0.19, 95% CI 0.13 - 0.27, respectively). Probabilities among mixed breastfeeders surpassed both groups, reaching 0.26 (95% CI 0.21 - 0.32) by 6 months Cumulative probability of HIV infection by 15 months was 0.25 (95% CI 0.16 - 0.34). This was still lower than among other breastfeeders – 0.36 (95% CI 0.27 - 0.45). In multivariate analysis EBF was associated with a significantly lower risk of HIV infection (adjusted HR 0.56, 95% CI 0.22 - 1.42) than mixed BF (adjusted HR 0.87, 95% CI 0.33 - 2.33) **Main messages: Pattern of infant feeding affects transmission; EBF was associated with a lower risk of HIV transmission than mixed feeding**
2003 Richardson *et al.*[40] Nairobi, Kenya Prospective RCT Nested case control study within RCT of BF and FF	None	None	Mother's CD4 count <400/µl was associated with 3-fold higher breastmilk infectivity per litre of breastmilk ingested and per day of BF by the infant compared with CD4 cell count ≥400 **Main messages: Breastmilk infectivity remains high throughout the BF period. Lowering breastmilk viral load during BF is a potential strategy to reduce breastmilk infectivity**
2004 BHITS study group[41] Meta-analysis, 9 randomised placebo-controlled trials	None	None	Overall estimated risk of late postnatal (negative at or before 4 weeks followed by positive results) HIV transmission was 8.9 transmissions per 100 child-years of BF The cumulative probability of late postnatal transmission at 18 months was 9.3% **Main messages: Cases of postnatal transmission continued to occur throughout the BF period. Breastmilk transmission remained fairly constant throughout the BF period**
2005 Illiff *et al.*[25] Zimbabwe RCT Mothers randomised to 1 of 4 vitamin A treatment groups All mothers BF	None	None	Compared with EBF, early mixed feeding was associated with a 4.03 (95% CI 0.98 - 16.61), 3.79 (95% CI 1.40 - 10.29) and 2.60 (95% CI 1.21 - 5.55) greater risk of postnatal HIV transmission at 6, 12 and 18 months, respectively Predominant BF was associated with a 2.63 (95% CI 0.59 - 11.66), 2.69 (95% CI 0.95 - 7.63, and 1.61 (95% CI 0.72 - 3.64) trend towards greater postnatal transmission risk at 6, 12 and 18 months, respectively, compared with EBF **Main messages: EBF was associated with a lower risk of HIV transmission compared with mixed feeding. Predominant BF also tended to carry higher risks of transmission compared with EBF**
2006 MASHI study[30] Botswana RCT	AZT for 6 months FF	BF Infant AZT	**Main messages: FF was associated with significantly higher rates of infant mortality and severe pneumonia and diarrhoea by 6 months, particularly among HIV-infected children** **24-month HIV-free survival did not differ between arms** With the exception of grade 3/4 pneumonia and in the context of weaning at 6 months by the BF arm, differences by feeding arm were attenuated by 24 months

TABLE I. KEY STUDIES THAT HAVE CONTRIBUTED TO THE BODY OF KNOWLEDGE ON HIV AND INFANT FEEDING (CONTINUED)

Year, author, setting, study design, and characteristics of population	Regimens		Results and major contribution
	Mother	Baby	
2007 Coovadia *et al.*[23] Hlabisa – rural area, South Africa POC AFASS-guided feeding	Sd NVP	Sd NVP	14.1% (95% CI 12.0 - 16.4) of exclusively BF infants were infected with HIV-1 by age 6 weeks and 19.5% (17.0 - 22.4) by 6 months Transmission risk was significantly associated with maternal CD4 cell counts below 200 cells/µl (adjusted HR 3.79; 2.35 - 6.12) and birth weight less than 2 500 g (1.81, 1.07 - 3.06). Kaplan-Meier estimated risk of acquisition of infection at 6 months of age was 4.04% (2.29 - 5.76) BF infants who also received solids were significantly more likely than EBF children to acquire infection (HR 10.87, 1.51 - 78.00, p=0.018), as were infants who at 12 weeks received both breast-milk and formula milk (1.82, 0.98 - 3.36, p=0.057) Cumulative 3-month mortality in EBF infants was 6.1% (4.74 - 7.92) v. 15.1% (7.63 - 28.73) in infants given replacement feeds (HR 2.06, 1.00 - 4.27, p=0.051) **Main messages: Early introduction of solids increased transmission risks, as did mixed feeding. 3-month mortality was highest in infants receiving no breastmilk compared with infants who were EBF; low maternal CD4 cell count increased risk of infant HIV acquisition**
2007 Kuhn *et al.* (ZEBS)[26] Zambia Epidemiological study nested within a RCT evaluating the safety and efficacy of early weaning	Sd NVP	Sd NVP	Postnatal HIV transmission before 4 months was significantly lower (p=0.004) among EBF (0.040, 95% CI 0.024 - 0.055) than non-EBF infants (0.102, 95% CI 0.047 - 0.157); time-dependent relative hazard (RH) of transmission due to non-EBF = 3.48 (95% CI 1.71 - 7.08) There were no significant differences in the severity of disease between EBF and non-EBF mothers, and the association remained significant (RH=2.68, 95% CI 1.28 - 5.62) after adjusting for maternal CD4 count, plasma viral load, syphilis screening results and low birth weight **Main messages: Non-EBF more than doubles the risk of early postnatal (by 4 months) HIV transmission. Early cessation of breastfeeding increases morbidity and mortality risks**
2008 SWEN[19] Ethiopia, Uganda and India 3 similar RCTs All BF	**C:** sd NVP **Int:** sd NVP	**C:** sd NVP **Int:** sd NVP + extended daily NVP until 6 weeks	There was a 46% decrease in postnatal HIV infection at age 6 weeks in infants uninfected at birth, with extended nevirapine compared with the control arm. There was a continued risk of postnatal HIV transmission after the regimens were discontinued in infants who continued to be breastfed; however this risk was similar in both arms **Main messages: Postnatal infant NVP for 6 weeks reduced transmission compared with sd NVP, and improved 6-month HIV-free survival. Transmission risk continued after NVP was stopped**
2008 Post Exposure Prophylaxis to the Infant (PEPI) trial[17] Malawi RCT All BF	**C:** sd NVP **Int 1:** sd NVP **Int 2:** sd NVP	**C:** sd NVP + 1 week AZT **Int 1:** sdNVP + 14 weeks daily NVP **Int 2:** sd NVP + 14 weeks NVP and AZT	At 9 months, the estimated rate of HIV-1 infection (the primary end-point) was 10.6% in the control group compared with 5.2% in the extended-nevirapine group (p<0.001) and 6.4% in the extended-dual-prophylaxis group (p=0.002). There were no significant differences between the two extended-prophylaxis groups. There was a continued risk of postnatal HIV transmission after the regimens were discontinued in infants who continued to be breastfed; however this risk was similar in both arms **Main messages: Extended prophylaxis with NVP or with NVP and AZT for the first 14 weeks of life significantly reduced postnatal HIV-1 infection in 9-month-old infants. 9-month HIV-free survival was higher among infants who received 14 weeks' postnatal prophylaxis compared with control infants who only received 1 week's ARV cover (adjusted HR=0.001 for the 14-week postnatal infant NVP prophylaxis group, and adjusted HR=0.004 for the 14-week postnatal infant NVP + AZT prophylaxis group – both compared with control)**

TABLE I. KEY STUDIES THAT HAVE CONTRIBUTED TO THE BODY OF KNOWLEDGE ON HIV AND INFANT FEEDING (CONTINUED)

Year, author, setting, study design, and characteristics of population	Regimens		Results and major contribution
	Mother	Baby	
2008 MITRA study[15] Dar es Salaam, Tanzania POC All BF	AZT/3TC to mothers from 36 weeks' gestation to 1 week postpartum	AZT/3TC to infants for 1 week followed by daily 3TC to infants for a maximum of 6 months	Cumulative HIV transmission was 3.8% at 6 weeks and 4.9% at 6 months of age. The risk of postnatal infection from 6 weeks to 6 months was 1.1% **Main messages: Infant prophylaxis for 6 months resulted in a low risk of HIV transmission through breastmilk**
2009 Kesho Bora[14] 5 sites in Burkina Faso, Kenya and South Africa HIV-infected women with CD4 200 - 500 cells/µl randomised RCT All BF	**C:** AZT started 28 - 36 weeks + sd NVP at labour + 1 week PN AZT/3TC **Int:** HAART started 28 - 36 weeks preg. through 6 months postpartum	sd NVP + 1 week AZT in both arms	The rates of HIV infection at birth were similar in both arms: 1.8% in the HAART arm versus 2.2% in short-course AZT arm At age 6 months cumulative HIV infection rates were 4.9% in the maternal HAART arm, compared with 8.5% in the short-course AZT arm Between 6 weeks and 6 months the postnatal infection rate was 1.6% in the maternal HAART arm compared with 3.7% in the short-course AZT arm without extended prophylaxis The rate of infection after the prophylaxis/HAART was discontinued was similar in both arms **Main messages: A maternal HAART arm was more efficacious than short-course regimens**
2009 Mma Bana[18] Botswana RCT HIV-infected pregnant women with CD4 cell counts >200 cells/µl were randomised. RCT All BF	**Int 1:** triple nucleoside HAART regimen **Int 2:** protease inhibitor-containing HAART regimen started 26 - 34 weeks through 6 months of BF	Sd NVP + 4 weeks AZT	Rates of viral suppression at delivery and during breastfeeding were similar between the 2 HAART regimens. The cumulative infant HIV infection rate at age 6 months was 1% (95% CI 0.5 - 2%) with only 2 infections (0.4% transmission) in 553 infants with no difference between the 2 arms **Main messages: Maternal HAART regimens were efficacious in reducing postnatal transmission in mothers with CD4 cell count >200 cells/µl**
2009 MITRA plus[16] Dar es Salaam, Tanzania POC All BF	HAART to pregnant women starting at 34 weeks and continuing through 6 months of breastfeeding		Cumulative risk of HIV infection was 5% at 6 months and 6% at 18 months of age. The risk of postnatal infection between 6 weeks and 6 months was only 1% **Main messages: Maternal HAART during BF reduced postnatal transmission through breastmilk**
2009 Breastfeeding, Antiretrovirals and Nutrition (BAN) study[13] Malawi RCT Women with CD4 cell counts >250 cells/µl at delivery and no previous antenatal prophylaxis	**C:** intrapartum sd NVP + 1 week AZT/3TC **Int 1:** C regimen + HAART from 1 week till 6 months postpartum **Int 2:** C regimen	**C:** sd NVP + 1 week AZT/3TC **Int 2:** daily infant NVP from 1 week to 6 months postpartum	The cumulative probability of HIV infection at age 6 months in infants uninfected with HIV at birth was 6.4% in the control arm, 3.0% in the maternal HAART arm (p=0.0032 v. controls), and 1.8% in the infant NVP arm (p<0.001 v. control arm). The rates were not statistically different between the 2 intervention arms, although the study was not powered to detect a difference between the arms **Main messages: Maternal HAART for 6 months and infant NVP for 6 months were equally efficacious in reducing postnatal HIV transmission through breastmilk at 6 months, although the data suggest a trend favouring infant NVP from 1 to 6 months over maternal HAART from 1 week to 6 months (p=0.0698)**

POC = prospective observational study; RCT = randomised controlled trial; CC = case control study; C = control group; Int = intervention group; BF = breastfeeding; FF = formula feeding; EBF = exclusive breastfeeding; EFF = exclusive formula feeding; NVP = nevirapine; AZT = zidovudine; 3TC = lamivudine; Sd = single-dose.

beneficial and supported by exclusive or predominant breastfeeding to maximise infant HIV-free survival.

One of the current gaps in the literature is that no study has examined whether HIV-free survival differs between HIV-exposed infants who appropriately avoid all breastfeeding, and breastfeeding HIV-exposed infants who receive postnatal prophylaxis to reduce postnatal transmission. This work still has to be done.

While regimens to minimise postnatal HIV transmission are still being finalised (particularly in the public sector), health care providers and mothers need to be supported so that current feeding recommendations maximise HIV-free survival. These recommendations are explained in the next section.

CURRENT INTERNATIONAL AND NATIONAL FEEDING RECOMMENDATIONS, AND THE BASIS THEREOF

In 2005 the Lancet Child Survival series showed that universal coverage with EBF for 6 months and continued breastfeeding – i.e. breastmilk and complementary foods – up to 1 year may prevent 13% of under-5 deaths globally, even in the presence of HIV.[21]

Subsequently the Lancet Nutrition series showed that in the first 6 months of life EBF has far greater child survival benefits compared with predominant breastfeeding (feeding breastmilk and non-nutritive liquids), partial breastfeeding and not breastfeeding for all-cause mortality (odds ratio (OR) 1.48 (95% confidence interval (CI) 1.13 - 1.92), OR 2.85 (95% CI 1.59 - 5.10), OR 14.40 (95% CI 6.09 - 34.05), respectively), diarrhoea mortality (OR 2.28 (95% CI 0.85 - 6.11), OR 4.62 (95% CI 1.81 - 11.77), OR 10.53 (95% CI 2.80 - 39.64)) and pneumonia mortality (OR 1.75 (95% CI 0.48 - 6.43), OR 2.49 (95% CI 1.03 - 6.04), OR 15.13 (95% CI 0.61 - 373.84)) in resource-limited settings.[22]

Despite these benefits of EBF, research highlighted in Table I also shows that any breastfeeding (including EBF) carries a risk of postnatal HIV transmission, which is largest for mixed feeding and smallest for EBF.[23-26] HIV infection therefore presents new challenges for infant feeding, which have often been explained as two sides of a scale – one side is weighed down by the risk of HIV transmission through breastfeeding, and the other is weighed down by the risk of morbidity and mortality from common childhood illnesses as a result of not breastfeeding. This risk of mortality as a result of not breastfeeding has been documented among HIV-exposed infants in numerous sub-Saharan settings, including South Africa.[23, 27-30]

Furthermore, Doherty *et al.* show that inappropriate decisions to formula feed and inappropriate decisions to breastfeed were associated with an increased hazard of HIV or death compared with appropriate decisions to formula feed (adjusted hazard ratio (HR) 3.63 (95% CI 1.48 - 8.89) and 3.35 (95% CI 1.25 - 8.96) compared with 1, respectively).[31]

CURRENT RECOMMENDATIONS

In an attempt to be pragmatic, to minimise breastmilk transmission of HIV and maximise HIV-free survival, the World Health Organization (WHO), UNICEF and Inter-agency Task Team (IATT) recommended between 2006 and November 2009 that feeding decisions in HIV-positive women should depend on the mother's health status, the local situation, the health services available and the counselling support she is likely to receive.[32] Until 30 November 2009 the IATT recommended that EBF for 6 months should be instituted unless replacement feeding (avoiding breastmilk) is **A**cceptable, **F**easible, **A**ffordable, **S**ustainable and **S**afe (commonly referred to as the AFASS criteria). At 6 months, if replacement feeding is still not AFASS, continuation of breastfeeding with additional complementary foods is recommended. All breastfeeding in HIV-positive women should stop once a nutritionally adequate and safe diet without breastmilk can be provided. On 30 November 2009, the WHO released revised rapid guidance on HIV and infant feeding (available from http://www.who.int/child_adolescent_health/documents/9789241598873/en/index.html). These state, *inter alia*, that mothers known to be HIV infected (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life.

Breastfeeding should then only stop once a nutritionally adequate and safe diet without breastmilk can be provided. Mothers known to be HIV infected who decide to stop breastfeeding at any time should stop gradually within 1 month. Mothers or infants who have been receiving ARV prophylaxis should continue prophylaxis for 1 week after breastfeeding is fully stopped. Stopping breastfeeding abruptly is not advisable. Mothers known to be HIV infected should only give commercial infant formula milk as a replacement feed to their HIV-uninfected infants or infants who are of unknown HIV status, when specific conditions are met (referred to as AFASS – affordable, feasible, acceptable, sustainable and safe – in the 2006 WHO recommendations on HIV and Infant Feeding).

While the IATT 2006 - 2009 recommendations have been accepted by most resource-limited countries, countries still need to discuss the 2009 revisions and then amend their policies. Fig. 1 lists the current South African PMTCT guidelines on infant feeding in the context of HIV.[33] These are similar to the guidelines followed in many resource-limited countries.

HIV-negative women

- At every antenatal visit HIV-negative women or women of unknown HIV status (every effort should be made to get all pregnant women tested or re-tested as stated in the testing section of this document) should be counselled to exclusively breastfeed their babies during the first 6 months of life and continue breastfeeding for at least 2 years.

HIV-positive women

- At every antenatal visit HIV-positive women should be counselled on infant feeding options.
- Each pregnant HIV-positive woman should receive at least four antenatal counselling sessions on infant feeding.
- The feeding options for the first 6 months of life are exclusive breastfeeding or exclusive formula feeding. All HIV-positive infants should continue breastfeeding for at least 2 years, regardless of whether the mother meets the AFASS criteria.
- For each woman, the **A**cceptability, **F**easibility, **A**ffordability, **S**afety and **S**ustainability criteria **(AFASS)** should be assessed and discussed, and the woman should be assisted to make the feeding choice that would be most appropriate for her individual situation.

Fig. 1. Current (2008) South African PMTCT feeding recommendations.[33]

The IATT 2006 - 2009 recommendations need to be implemented while countries finalise their new policies on postnatal prophylaxis and infant feeding. Although new policies – which will stem from recent evidence (Table I) and the WHO rapid guidance – still need to be debated and finalised, aspects of the IATT 2006 - 2009 recommendations on infant feeding and HIV will still be relevant henceforth. For example, if women meet the AFASS criteria they should still be advised not to breastfeed so that postnatal HIV transmission is eliminated; if women do not meet the AFASS criteria then the new policy may advise breastfeeding for 6 months with an ARV regimen that continues throughout the breastfeeding period. From a child survival perspective EBF has been recommended for mothers who do not meet the AFASS criteria. However, in most African settings EBF is not a normative cultural practice in the absence of intense support. Ghuman *et al.* showed that the EBF rate among women of unknown HIV status – living in a high-HIV prevalence area – was 18% at 14 weeks,[10] and Goga *et al.* showed that only 18% of HIV-positive breastfeeding women practised EBF at 12 weeks in a PMTCT programme setting.[11] Bland *et al.* (the Vertical Transmission Study) were able to increase EBF rates to 40% at 6 months following an intense peer counselling intervention comprising approximately 20 home-based visits starting antenatally (4 visits) until 6 months after delivery.[12] However, it is questionable whether this intervention is replicable in a programmatic setting. More recently a pooled analysis of data from the Vertical Transmission Study (South Africa) and Ditrame Plus Study (Cote d'Ivoire) showed that postnatal HIV transmission rates were not significantly different among infants who had been exclusively breastfed or predominantly breastfed for the same time period; however, infants exposed to solids at least once during the first 2 months of life were 2.9 (95% CI 1.1 - 8.0) times more likely to become HIV infected postnatally compared with infants who had never received solids this early.[34] This analysis did not compare HIV-free survival among predominantly or exclusively breastfed infants, but it does suggest that if EBF is not socially or culturally feasible among breastfeeding HIV-positive mothers, the next best option is predominant breastfeeding. Mixed feeding with the early introduction of solids is the most risky for transmission.

The following section provides recommendations on how to implement feeding recommendations that assess the appropriateness of feeding options (AFASS), as this has been a stumbling block. It also suggests how safe (exclusive or predominant) infant feeding can be supported.

HOW TO IMPLEMENT THE FEEDING RECOMMENDATIONS

In view of recent data highlighting the risks of inappropriate feeding choices with regard to HIV-free survival,[31] much attention needs to be given to how HIV-positive women make their feeding choices. To assess AFASS a checklist can be used (Table II). If there is any 'No' in the 'EBF for 6 months' column, advise the mother to exclusively breastfeed for 6 months. If all responses are 'Yes', advise her to avoid all breastfeeding.

In a recent review of solutions to operational challenges in PMTCT,[35] a novel '5-finger approach' to assess AFASS and facilitate appropriate infant feeding choices has been described by Coutsoudis and Kroon. An example of the 5-finger approach, which is based on current literature,[31] is illustrated in Fig. 2 and can be used by doctors, nurses and lay counsellors. Fig. 2 is in the process of being revised by Coutsoudis and Kroon so that the 'Breast is Best' logo is not so prominent. Readers interested in using Fig. 2 should contact Coutsoudis and Kroon for updated versions.

Regardless of the method used to assess AFASS, appropriate infant feeding choices should be encouraged to maximise child survival in the context of PMTCT.

TABLE II. ASSESSING AFASS CRITERIA

Questions that can be used to assess AFASS	Most suitable feeding option	
	EBF for 6 months if NO to ANY of these questions	Avoiding all breastfeeding: Exclusive formula feeding for 6 months if YES TO ALL of these questions
Can the mother avoid all breastfeeding in her current social and cultural context?	NO	YES
Does the family/person the woman stays with know that she is HIV positive?	NO	YES
Can the woman overcome or deal with any stigma or discrimination if she were to choose to avoid all breastfeeding?	NO	YES
Will the woman be able to go to the clinic to collect formula milk regularly?	NO	YES
Will the woman have money for transport to collect milk or to buy milk if the supply runs out or to take the infant to a clinic if he/she gets diarrhoea?	NO	YES
Does the woman or caregiver have enough time, knowledge, skills, resources and support to correctly prepare breastmilk substitutes?	NO	YES
Will the woman be able to prepare night feeds easily?	NO	YES
Is the mother able to feed the infant 8 - 12 times in 24 hours?	NO	YES
Will the woman be able to regularly buy utensils needed to prepare formula milk?	NO	YES
Will the woman be able to get a continuous, uninterrupted supply of formula milk AND water AND fuel?	NO	YES
Is there piped water in the house or yard that can be accessed regularly?	NO	YES
Will the woman be able to wash her hands before preparing each feed and prepare each feed with boiled water and clean utensils?	NO	YES
Will the woman be able to store formula milk correctly and hygienically?	NO	YES

Lastly, the acronym SSSUPPORT (Table III) should be taught or displayed in all health facilities to remind health workers about their responsibilities towards optimising child survival through appropriate infant feeding counselling in the context of HIV.

SUMMARY AND CONCLUSIONS

Postnatal maternal or infant ARV regimens reduce postnatal HIV transmission through breastmilk. Maternal postnatal regimens appear as efficacious as infant postnatal regimens; however, data suggest that there may be a trend favouring infant nevirapine over maternal HAART (both used from 1 week to 6 months after delivery). The protective effect of regimens stops once the regimens stop, if breastfeeding continues. Any of the new regimens should be implemented among breastfeeding HIV-positive mothers without further delay where the human resource, financial and socio-cultural capacity exists to do this, e.g. in private sector facilities, despite the inherent inequity in this approach.

For resource-limited public health settings three main issues need to be considered when deciding on which ARV regimen to include in a national policy: (*i*) the basic science: efficacy and possible effectiveness of various postnatal prophylactic regimens using HIV transmission and HIV-free survival as the main outcomes; (*ii*) the feasibility of each regimen, from a user perspective; and (*iii*) the feasibility of each regimen from a health system/service perspective. Work needs to be undertaken urgently to examine these issues.

While stakeholders engage in discussions about which is the best regimen to include in national policy on minimising postnatal transmission, **SSSUPPORT** should be given to all HIV-positive women to improve infant outcomes and reduce postnatal transmission: **S**creen all women for HIV; **S**end off CD4 cell counts on all HIV-positive women; **S**creen all HIV-positive women for AFASS using a standardised tool (e.g. Table II/Fig. 2); **U**nderstand the woman's personal and socio-cultural context; **P**romote exclusive or predominant breastfeeding if all AFASS criteria are not met; **P**romote exclusive

Fig. 2. A 5-finger method of assessing AFASS criteria developed by Anna Coutsoudis and colleagues (Department of Paediatrics and Child Health, UKZN) and Max Kroon, Mowbray Maternity Hospital, Western Cape. Note that this 5-finger approach is evolving, and is being amended to reduce the size of the 'Breast is Best' caption and text. Readers should contact Coutsoudis and Kroon for updated versions.

formula feeding if all AFASS criteria are met; **O**rganise supplies of formula milk and co-trimoxazole; **R**eview mothers and infants in the first 3 days after delivery, in the first 2 weeks postnatally and monthly thereafter, and review health and feeding practices, regardless of feeding choice, at every visit; and lastly **T**reat all pregnant women with HAART if they meet national criteria for HAART initiation.

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TABLE III. KEY MESSAGE TO PROMOTE SAFE INFANT FEEDING AND IMPROVE HIV-FREE SURVIVAL

Support	Without prophylaxis to reduce postnatal transmission through breastmilk	Additional steps if prophylaxis to reduce postnatal HIV transmission through breastmilk becomes policy
S **S** **S**	Screen all women for HIV Send off CD4 cell counts on all HIV-positive women Screen all HIV-positive women for AFASS	
U	Understand the mother's personal and socio-cultural context	
P	Promote exclusive or predominant breastfeeding if all the AFASS criteria are not met	PLUS start postnatal prophylactic regimens to minimise postnatal HIV transmission
P	Promote exclusive formula feeding if all the AFASS criteria are met	
O	Organise supplies: of formula milk if mothers meet AFASS and choose to formula feed of co-trimoxazole for infants from 6 weeks	PLUS supplies: of prophylactic antiretrovirals if mothers do not meet AFASS
R	Review mothers and infants in the first 3 days post-natally, in the first 2 weeks postnatally and monthly thereafter Review mother's and infant's health, and infant feeding practices/techniques, regardless of feeding choice	PLUS adherence to any regimens
T	Treat all mothers and children with antiretroviral therapy according to updated recommendations	

Adapted from Goga *et al.*[11] and Jackson *et al.*[42]

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GUIDELINES FOR ANTIRETROVIRAL THERAPY IN CHILDREN – NOVEMBER 2009 VERSION

These guidelines are intended to provide paediatric HIV antiretroviral treatment (ART) recommendations for both the public and private sectors.

ART in children follows the same principles as in adults, and treaters should not be daunted by some of the differences, which include more frequent dose adjustments, liquid formulations occasionally being poorly palatable, and the dependence of children on adult caregivers for receiving medication. These should not be viewed as obstacles, and everything should be done to assist the process of treating children.

Since the last publication of these guidelines there have been pivotal paediatric studies that have necessitated the updating of paediatric guidelines in South Africa.

1. GOALS OF THERAPY

- Durable suppression of viral load (VL) (undetectable VL using an ultrasensitive assay)
- Restoration or preservation of immunological function (CD4+ count)
- Sustained improvement in clinical symptoms and quality of life
- Reduction in morbidity and mortality.

1.1 FAMILY TREATMENT

Since HIV is usually a disease occurring within families, the following are important:

- Always enquire about the health and HIV status of the caregivers and other family members.
- Encourage and assist caregivers to start ART if required; ideally families should receive treatment simultaneously in the same facility to avoid inconvenience and unnecessary expense for patients.
- HIV testing should be offered and recommended for other family members if their status is unknown.
- Ascertain and encourage HIV disclosure status of caregivers themselves, the child and other family members.

2. ADHERENCE

High levels of adherence to antiretroviral therapy (ART) are vital for treatment success. The goal is for the patient to receive 100% of scheduled doses. Factors that impact on adherence include:

- Parental/caregiver education: they must understand that poor adherence is the single most important factor for drug failure and resistance, leading to loss of future therapeutic options.
- A good health care provider-patient relationship underpins adherence.
- Motivation and commitment of caregiver/parent to the child's lifelong therapy.
- Address any social issues as appropriate.
- Although unpredictable events can acutely impact on adherence (e.g. severe illness or death of a parent), frequent visits and good communication may help to anticipate and pro-actively plan for such events

Conveners: Prof. Mark Cotton and Dr Leon Levin

Writing Committee: Prof. Mark Cotton, Dr Leon Levin and Dr Tammy Meyers

Expert Panel Members: Profs Ashraf Coovadia, Mark Cotton, Brian Eley, Glenda Gray, Prakash Jeena, Simon Schaaf; Drs Moherndran Archary, Lee Fairlie, Ute Feucht, Leon Levin, Pippa MacDonald, Tammy Meyers, Harry Moultrie, Kimesh Naidoo, James Nuttall, Helena Rabie, Paul Roux , Lizzy Tabane, Avy Violari, Marnie Vujovic; Ms Liezel Pienaar

International Reviewers: Drs Stephane Blanche, Ann Melvin, Gareth Tudor Williams, Andrew Wiznia

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TALKING ABOUT ADHERENCE

Working with the client

A short checklist of points should include:

- Checking caregiver's capacity to understand treatment plan/adherence (intellectual/developmental level, literacy)
- Checking the basic facts about ART
- Explaining adherence and why it is important
- Explaining common ART side-effects and likely course
- Explaining that symptoms associated with other illnesses (i.e. vomiting, diarrhoea, cough, fever, rash) overlap with drug toxicity and are not a reason to stop therapy. However, if an acute illness (acute gastro-enteritis) occurs and the child is unable to tolerate medications, it is permissible to stop all meds for a short period of time
- Exploring the caregiver's readiness to start the child on antiretroviral therapy
- Assessing the level of commitment to ART adherence
- Assessing the caregiver's perception of the advantages and disadvantages of being on ART.

Discussion should include an assessment of the caregiver's psychosocial situation. This covers:

- Exploration of the caregiver's lifestyle (e.g. work, daily routine, sleep, other responsibilities)
- Exploration of the caregiver's personality traits (e.g. sense of organisation, self-discipline and responsibility)
- Assessment of the caregiver's own HIV status and health and lifestyle choices (use of alcohol and drugs) (remember – HIV infection in adults not yet on ART can cause cognitive impairment)
- Possible use of alternative/complementary medicine
- Exploration of the caregiver's financial and material resources.

It is also necessary to explore possible barriers to adherence as well as sources of support, including:

- Discussion around disclosure (e.g. how much the child knows about own status/how much other household members know about child's status/reasons for not wanting to disclose to child/others if applicable). Disclosure is an evolving process requiring an active plan and involvement of the parent/caregiver
- Exploration of the current and potential sources of support
- Problem solving with regard to barriers
- Anticipation of events that might present an obstacle to adherence, e.g. school trips, visits to grandparents.

Finally, a specific adherence plan is developed in collaboration with the client (and child where appropriate). The plan should specify:

- The treatment regimen (specifics of medication, doses and the intervals at which the medication should be given). Remember that the same drug may have many names (formula, generic, trade, fixed-dose combinations), which may be confusing to patients and families
- Possible side-effects, what to do and who to contact in the case of serious side-effects
- Ways of integrating treatment into the daily routine of the caregiver/child, especially the specific times the medication will be given.

The plan should be individualised and the health care professional is encouraged to provide practical aids and supportive information sheets. Demonstration of dosage and method of administration by the counsellor as well as by the caregiver is important.

Social disruption or catastrophic events can happen at any time and could affect adherence. Events such as loss of a caregiver or severe illness in a caregiver should be mentioned, with possible solutions.

Tips

In the case of school-age children and adolescents, it is important that adult caregivers are available to supervise. Routine is reassuring: caregivers should try to give medication in the same way, at the same time and in the same place every day. Caregivers should be encouraged to:

- Remind the child that medicines are important and will help to keep him or her from getting sick.
- Be positive and consistent when it comes to giving the child medicine.
- Always say something positive when the child has taken his/her medication.
- Reward the child with a sticker or a star on a record chart or calendar or other age-appropriate token.
- Allow the child to earn a special treat for sticking to his/her schedule (e.g. a small weekly treat and a bigger monthly treat. Avoid monetary rewards; a story or a favourite meal is more than adequate).
- Get other people who care about the child to encourage and reward him/her for taking medication.
- Anticipate and talk about possible problems before they arise.
- Be flexible with the treatment plan. Accommodate change (e.g. in the scheduled time of doses) if this would result in better adherence.
- Think of possible simplification of the regimen.
- Ask about any side-effects. Suggest ways to manage less serious side-effects and indicate the likelihood of relatively short duration.
- Ask about other medication that the child may be taking in order to avoid possible drug interactions and better co-ordinate dosing of all medications.
- Anticipate possible adherence fall-off during times of increased stress. Make time to discuss and deal with problems and feelings.
- Vomiting after taking medication: make sure that the caregiver knows that if a child vomits within 30 minutes of taking a medication the dose should be repeated.

Some tools and strategies

- Setting an alarm on an alarm clock
- Setting a cell phone alarm or reminder
- Using a pillbox
- Using a diary card
- Using a wall calendar
- Keeping a treatment diary
- Sending SMS reminders to the caregiver
- Using daily TV or radio programmes as cues
- Using mealtime (breakfast and supper) as a cue
- Having a treatment supporter
- Having a treatment buddy (another child, also on treatment)
- Keeping medication in a familiar place and not hidden or locked up
- Using directly observed treatment support (DOTS) as for TB if needed.

Additional factors enhancing adherence include:

- Children should be taught to swallow pills/capsules as early as possible (from about 4 years). This can be done using appropriately sized sweets. Liquid formulations may have an unpleasant taste or involve administering large volumes of liquids.
- Ideally the caregiver should identify and disclose to one other person in the home who can help with treatment (treatment buddy) as a back-up and enhance treatment support.
- Dosages of liquid formulations should be rounded up to a convenient volume.
- Syringes for liquid formulations should be marked at the correct dosage with a blade or permanent marker. Show the caregiver how to draw up the correct volume and expel excess air. Make sure that the syringes are appropriately cleaned.
- Each liquid medicine and its syringe should be colour-coded to prevent confusing medicines and dosages.
- Ensure that the caregiver's eyesight is adequate to administer medication accurately.
- Teach caregivers to open childproof containers.
- Medications should fit into the patient's lifestyle. For example, twice-daily medication does not have to be given strictly 12-hourly, rather at a convenient time. It is far better to give a dose later than usual than not to give the medication at all.
- Too many caregivers involved in administering medicines can be an obstacle to good adherence. A different caregiver accompanying the child to

each appointment is a warning sign, requiring exploration.

- Emphasise good adherence at each visit. It is useful to compare ART with therapy for diabetes and hypertension, both conditions requiring lifelong therapy and in which poor adherence is associated with disease progression. HIV is a chronic, manageable condition, with minimal morbidity, if the correct approach is taken.
- It is useful to monitor whether treatment is being collected.

3. INDICATIONS FOR STARTING ART IN CHILDREN

First assess the child clinically and stage the child according to the World Health Organization (WHO) Staging System (Table I) to determine whether the child needs ART or not (*note:* all infants diagnosed <12 months of age should be started on ART regardless of clinical or immunological staging). If the child is clinically well, CD4 testing will further ascertain whether the child needs ART.

TABLE I. WHO CLINICAL STAGING OF HIV/AIDS FOR CHILDREN WITH CONFIRMED HIV INFECTION

CLINICAL STAGE 1
Asymptomatic
Persistent generalised lymphadenopathy

CLINICAL STAGE 2
Unexplained persistent hepatosplenomegaly
Papular pruritic eruptions
Extensive wart virus infection
Extensive molluscum contagiosum
Fungal nail infections
Recurrent oral ulcerations
Unexplained persistent parotid enlargement
Lineal gingival erythema
Herpes zoster
Recurrent or chronic upper respiratory tract infections
(otitis media, otorrhoea, sinusitis or tonsillitis)

CLINICAL STAGE 3
Unexplained moderate malnutrition not adequately responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (above 37.5°C intermittent or constant for longer than one month)
Persistent oral candidiasis (after first 6 - 8 weeks of life)
Oral hairy leukoplakia
Acute necrotising ulcerative gingivitis or periodontitis
Lymph node tuberculosis
Pulmonary tuberculosis
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anaemia (<8 g/dl), neutropenia ($<0.5\times10^9$/l) and/or chronic thrombocytopenia ($<50\times10^9$/l)

CLINICAL STAGE 4i
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)
Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site)
Extrapulmonary tuberculosis
Kaposi's sarcoma
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Central nervous system toxoplasmosis (after 1 month of life)
HIV encephalopathy
Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than 1 month
Extrapulmonary cryptococcosis (including meningitis)
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated non-tuberculous mycobacterial infection
Cerebral or B-cell non-Hodgkin's lymphoma
Progressive multifocal leuco-encephalopathy
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy
HIV-associated rectovaginal fistula

The CHER Study[1] demonstrated that:

- By 6 weeks of age 20% of infants already had severe immunosuppression.
- In relatively asymptomatic infants, starting ART before 3 months of age reduced the mortality rate by 76%.

As a result of this research, all international ART guidelines now recommend immediate ART for all HIV-positive infants <12 months of age, irrespective of the clinical or immunological status (Table II). In the infant, ART should be started as soon as possible after diagnosis, preferably within 2 weeks.

4. INITIATION OF THERAPY

Note: **For young infants initiation of treatment should be rapid, with ongoing counselling while on ARVs.**

4.1 FIRST 1 – 2 VISITS

Full clinical examination, including accurate baseline weight, height, and for children <2 years, head circumference measurement. Bloods should be taken for HIV VL and CD4+ count.

Counselling and information – topics to be covered include:

- HIV prognosis
- Treatment options
- Adherence
- Drug formulations
- Taste issues (including taste test where appropriate)
- Initiate prophylaxis as indicated
- Ensure family/caregivers have contact details for staff in case of any questions/adverse events.

4.2 NEXT VISIT

If therapy is indicated and if the family is adequately counselled and able to continue to maintain adherence, dispense drugs. Graphically illustrate the drugs and how and when to take them, preferably with actual drugs or samples. Consider observing initial administration of the drugs.

TABLE II. CRITERIA FOR ART INITIATION

Age	Clinical stage	CD4 criteria
<1year	All infants	Any CD4
1 - 5 years	WHO stage III, IV	CD4 ≤25% Absolute CD4 <750 cells/µl
>5 years	WHO stage III, IV	CD4 <350 cells/µl

4.3 DAY 2 OF TREATMENT

If possible, a quick phone call to make sure that everything is in order is a good idea.

4.4 1 – 2 WEEKS LATER

A phone call to the caregiver/parent is recommended to discuss tolerance and adherence issues. The government roll-out programme recommends a 2-week visit where adherence is discussed and medication technique is checked.

4.5 ONE MONTH AFTER STARTING TREATMENT

The clinician should conduct a general examination and draw blood to monitor drug toxicity (in national Department of Health (NDoH) guidelines, only if on tuberculosis (TB) treatment or on zidovudine (AZT)).

Tolerance and adherence issues should be discussed. It may be useful to ask how many doses have been missed in the last 3 days, and how many in the last month.

In young children weight gain can be surprisingly rapid. Check whether doses need to be increased.

4.6 THREE MONTHS AFTER STARTING TREATMENT

The clinician should conduct a general examination and draw blood to monitor drug toxicity. Check weight and alter doses accordingly.

Bloods should also be taken for HIV VL and CD4+ count. In the NDoH guidelines, bloods would only be drawn if clinically indicated for suspected toxicity, if on AZT or if co-treated for TB.

Adverse effects, tolerance and adherence issues should be discussed with the caregiver.

4.7 THREE-MONTHLY THEREAFTER

The clinician should conduct a general examination and draw blood for drug toxicity, HIV VL and CD4+ count. NDoH guidelines recommend 6-monthly bloods with 3-monthly clinical checks. Check weight and alter doses accordingly. If the patient's results remain stable, clinical examinations and blood tests can be carried out 6-monthly, but children aged less than 2 years need to be seen at least 3-monthly to adjust drug doses according to growth.

Discuss adverse effects, tolerance and adherence issues with the caregiver at every visit.

5. MONITORING: SPECIAL CONSIDERATIONS FOR CHILDREN (TABLE III)

5.1 VIRAL LOAD

Recent reports on outcomes on ART of children from resource-poor centres demonstrate that undetectable VLs are initially achieved in over 80% of treatment-naïve children.[2]

VLs should be measured at baseline and then 3 - 6-monthly. In the NDoH guidelines VL testing is recommended at 6-monthly intervals unless there is a clinical indication to do it earlier. A recent meta-analysis suggests that VL monitoring at intervals of ≥3 months was associated with a significantly lower risk of resistance mutations at the time of failure.[3]

Therapeutic options for children are currently limited. The decision to switch therapy because of suboptimal response should therefore be carefully considered and balanced against the risk of accumulating additional resistance in a non-suppressive regimen.

Although there is no consensus, a growing number of international experts advise aggressively achieving and maintaining viral suppression.

Note:

- A repeat test is recommended whenever a routine measurement yields an unexpected result. It is usually not worth doing routine plasma HIV RNA levels during an intercurrent infection. Additional non-routine testing may be indicated if the clinical condition changes.
- Two measurements should be performed 1 month apart before instituting changes.
- VLs can be temporarily raised for up to a month after intercurrent infection or vaccination.
- Patients should be sequentially tested using the same method and the same laboratory.
- The NDoH has decided to omit the baseline VL in order to save costs. Since the baseline VL doubles as a confirmatory test for infants diagnosed by PCR, it is strongly recommended that the baseline VL still be done in infants diagnosed by PCR.

5.2 CD4+ LYMPHOCYTE COUNTS AND PERCENTAGES

The CD4+ count should be measured with the VL, except when the VL is repeated for an unexpected result. Absolute CD4+ lymphocyte counts are much higher in infancy than adulthood, but the CD4+ percentage is more constant, although also higher in children <2 years. CD4+ percentages may be easier to work with, but CD4+ counts should also be used. Over the age of 5 years, adult cut-offs using CD4 counts can be used for therapeutic decision making. Lymphopenia and lymphocytosis may over- or understate CD4 percentages or counts.

CD4+ counts/percentages are useful for monitoring response to ARVs. VL changes will typically precede changes in CD4 counts. CD4+ counts can be temporarily lowered by intercurrent infections or vaccinations, taking up to a month to recover.

Although there is a strong association between CD4+ depletion and opportunistic diseases, *Pneumocystis jirovecii* pneumonia (PCP) may occur in the first year of life despite 'normal' counts for age.

5.3 HEIGHT AND WEIGHT

The 'Road to Health' chart is a valuable tool for monitoring the well-being of children. Failure to maintain growth is suggestive of progressive HIV disease or superimposed infection such as TB.

TABLE III. ROUTINE MONITORING

Test	Baseline	2 weeks (NVP)	1 month*	3 months*	6 months	3 – 6–monthly thereafter*	Additional annual tests
Viral load	X†			X	X	X	
CD4	X			X	X	X	
FBC with differential	X		X	X	X	X	
ALT	X	X	X	X	X	X	
Cholesterol							X
Triglycerides							X
Glucose							X
Urine dipstix	X						X

*NDoH guidelines recommend 6-monthly monitoring.
†NDoH guidelines recommend **not** to do a baseline VL as a cost-saving practice. It is imperative that a baseline VL be done in **all** infants diagnosed on **PCR** as this doubles as a confirmatory test. Do not delay initiation of HAART while awaiting the confirmatory test result.
FBC = full blood count; ALT = alanine transaminase.

6. RECOMMENDED ARV REGIMENS

ART drugs are listed in Table IV, and dosages in Table V. Simplified weight-based dosing is set out in Fig. 1.

6.1 PREFERRED REGIMENS

First line

<3 years: 3TC + abacavir + lopinavir/ritonavir.

>3 years *and* >10 kg: 3TC + abacavir + efavirenz.

Alternate first line

<3 years: 3TC + stavudine + lopinavir/ritonavir.

>3 years *and* >10 kg: 3TC + stavudine + efavirenz.

This is the regimen currently recommended by the NDoH. There are major concerns about d4T toxicity, especially lipodystrophy. Stavudine should be changed to ABC at the first sign of lipodystrophy. In addition, zidovudine as part of second-line therapy will be compromised by resistance to stavudine.

Consider a boosted PI as the third drug in a child over 3 years exposed to SD-NVP or where there are concerns about adherence.

TABLE IV. ART DRUGS

Category I NRTI – thymidine base	Stavudine (d4T)* Zidovudine (ZDV)*
Category II NRTI – other	Didanosine (ddI)*† Lamivudine (3TC)* Emtricitabine (FTC) Abacavir (ABC)*
NtRTI	Tenofovir (TDF)†
Category III NNRTI	Nevirapine (NVP)* Efavirenz (EFV)¶ Etravirine (ETR)§
Category IV PI	Ritonavir (RTV)* Lopinavir/ritonavir (LPV/RTV)* Saquinavir (SQV) Indinavir (IDV)‡ Darunavir (DRV)§ Atazanavir (ATV)‡ Fosamprenavir (FPV)
Category V Integrase inhibitors	Raltegravir§
Category VI CCR5 inhibitors	Maraviroc§

*Available in paediatric formulations.
†Enteric-coated formulation for adults can be used (especially when given once instead of twice daily).
‡Not available in paediatric formulation.
¶EFV is only available in capsule form and tablet form. There are no data for children under 3 years of age or <10 kg.
§Paediatric dosage still uncertain. Requires Section 21 authorisation from the Medicines Control Council.
NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Rationale for choice of regimen

3TC and ABC backbone:

- Very good long-term data from PENTA 5.[4]
- Spares thymidine analogue for next regimen.
- Both drugs select for the same resistance pathway (M184V).
- ABC should only be used for first line (without genotyping) since >3 TAMS + M184V confers high level cross-resistance to ABC.
- Hypersensitivity is linked to HLA B*5701, which is extremely uncommon in the black population. The ARROW study of >1 200 HIV-infected children in Uganda and Zimbabwe had a hypersensitivity reaction rate of 0.2%.
- Tenofovir should not be used in children because of potential toxicity issues.

Lopinavir/ritonavir in children <3 years

Data show that young children have far better viral suppression on a boosted PI regimen than on an NNRTI regimen[5] (irrespective of single-dose NVP). In addition the IMPAACT P1060 study indicates that in SD-NVP-exposed infants, those starting NVP-based regimens have poorer virological outcomes than those starting a boosted PI regimen.[6]

7. DRUG INTERACTIONS

There are multiple opportunities for serious drug interactions. Treaters are advised to scrutinise package information and seek advice if uncertain.

- Rifampicin reduces levels of lopinavir, indinavir, saquinavir, atazanavir, fosamprenavir (PIs) and nevirapine and should not be used with any of these drugs.
- Efavirenz causes reduced levels of clarithromycin, but not azithromycin.
- Ritonavir should not be given with numerous drugs.
- Of the anti-epileptic drugs, sodium valproate is the safest to use with antiretrovirals.
- Ritonavir inhibits cytochrome P450 3A4, preventing metabolism of inhaled steroids, thereby facilitating systemic absorption and Cushing's syndrome. Rather use an NNRTI if the patient is on inhaled or nasal steroids, or consult the HIV Clinicians Society if this is not feasible.
- Oral contraceptives. There are limited data available on potential drug interactions between many ARVs (particularly some NNRTIs and RTV-boosted PIs) and hormonal contraceptives, which may modify their safety and effectiveness. RTV-boosted PIs are not recommended with combined or

TABLE V. DOSAGE AND FREQUENCY OF ARVs IN CHILDREN

Drug	Formulations	Dosage (per dose)	Frequency	Storage	Comments
Nucleoside reverse transcriptase inhibitors (NRTIs)					
Zidovudine (AZT, ZDV) Retrovir® generics	Susp: 10 mg/ml Caps: 100 mg, 250 mg, tabs 300 mg	Neonates 4 mg/kg/dose until 29 d, then 240 mg/m^2	2 2	Room temperature	May be taken with or without food
Didanosine (ddI) Videx® generics	Susp: 10 mg/ml Tabs: 25 mg, 50 mg, 100 mg, 150 mg Enteric-coated didanosine (EC) 250 mg, 400 mg	2 wks - 3 mo. of age: 50 - 100 mg/m^2/dose >3 mo. of age: 90 - 120 mg/m^2/dose	2 2 Can give total daily dosage × 1	Refrigerate suspension	Half hour before or 1 hour after meal Use single daily dose if necessary for adherence. Give at least 2 tabs of buffered formulation. Needs to be separated from PI by 1 - 2 hours. EC ddI still needs to be taken on empty stomach but can be given together with PI EC ddI capsules can be opened and sprinkled on food
Stavudine (d4T) Zerit® generics	Susp: 1 mg/ml Caps: 15 mg, 20 mg, 30 mg, 40 mg	Neonates <2 wks of age: 0.5 mg/kg/dose thereafter 1 mg/kg/dose (max 30 mg/dose)	2 2	Refrigerate suspension	May be taken with or without food. Capsules stable in water suspension for 24 hours at room temperature
Abacavir (ABC) Ziagen® generics	Susp: 20 mg/ml Tabs: 300 mg Kivexa® tabs = 600 mg ABC & 300 mg 3TC	All ages: 8 mg/kg/dose ≥25 kg: 1 tab or 2 tabs Kivexa® If ≥25 kg – 1 tab	2 2 1 1	Room temperature	May be taken with or without food **Watch for hypersensitivity reaction (HSR). Do not rechallenge if HSR occurs** If being given as suspension with 3TC, the two volumes should always be equal
Lamivudine 3TC (3TC®) generics	Susp: 10 mg/ml Tabs: 150 mg, 300 mg Kivexa® tabs = 600 mg ABC & 300 mg 3TC	Neonates: 2 mg/kg Paediatric (>1 month): 5 - 6 mg/kg ≥25 kg: 1 × 150 mg tab or 2 × 150 mg tab or 1 × 300 mg tab	2 2 2 1 1	Room temperature	May be taken with or without Can food use tablets from 25 kg
Nucleotide reverse transcriptase inhibitors (NtRTIs)					
Tenofovir (TDF) Viread®	Tablets 300 mg Truvada® = 300 mg TDF + 200 mg FTC Atripla®* = 300 mg TDF + 200 mg FTC + 600 mg EFV*	8 mg/kg/dose 8 mg/kg/dose of TDF component	1 1	Room temperature	**Should not be routinely used in children <18 years –** concerns about osteopenia and renal toxicity. May have a place in salvage in older children. Consult with a paediatric HIV expert. Viread tablets irregular shape – difficult to halve. May be taken with or without food. Dose adjustment required with renal impairment
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)					
Nevirapine (NVP) Viramune® generics	Susp: 10 mg/ml Tabs: 200 mg	Infants (>14 days) and children: 150 - 200 mg/m^2/dose Give dose once daily for first 14 days and increase to bd if no rash or severe side-effects occur	2	Room temperature	May be taken with or without food Skin rash usually occurs in 1st 6 weeks; do not increase dosage until rash resolves **Watch for liver toxicity** Try to maintain dosage >150 mg/m^2/dose bd

TABLE V. DOSAGE AND FREQUENCY OF ARVs IN CHILDREN (CONTINUED)

Drug	Formulations	Dosage (per dose)	Frequency	Storage	Comments
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)					
Efavirenz (EFV) Stocrin® generics	Tabs: 50 mg, 200 mg, 600 mg Caps: 50 mg, 200 mg	10 - <15 kg: 200 mg 15 - < 20 kg: 250 mg 20 - <25 kg: 300 mg 25 - <32.5 kg: 350 mg 32.5 - <40 kg: 400 mg >40 kg: 600 mg	1	Room temperature	No data <3 yrs and <10 kg Tablets cannot be crushed. Use generic capsules in children unable to swallow tablets. Capsules can be opened & given with food Give at night to avoid CNS side-effects **Anticipate** mild transient rash and CNS side-effects
Protease inhibitors (PIs)					
Atazanavir (ATV) Reyataz®	Capsules:150 mg, 200 mg	From 6 years of age: 205 mg/m^2 6 - 18 years: 15 - <25 kg: ATV 150 mg + RTV 80 mg 25 - <32 kg: ATV 200 mg + RTV 100 mg 32 - <35 kg: ATV 300 mg + RTV 100 mg >35 kg: ATV 300 mg + RTV 100 mg, both given once daily with food	1		**Ideally** should always be used with RTV boosting (unboosted ATV requires a higher dose and gives unpredictable plasma levels) Give with food Unconjugated hyperbilirubinaemia may occur and as long as the patient is comfortable with it, is not a reason to discontinue the drug
Fosamprenavir (fAPV) Telzir®	Tablets 700 mg Oral suspension, 50 mg/ml	2 - 5 years: 20 mg/kg/dose (max. dose 700 mg) + RTV 3 mg/kg/dose (max. dose 100 mg) 6-18 years: 18 mg/kg/dose (max. dose 700 mg) + RTV 3 mg/kg/dose (max. dose 100 mg)	2 2 2 2	Room temperature	**Ideally** should always be used with RTV boosting (unboosted fAPV requires a higher dose) Give suspension with food and tablets with or without food
Lopinavir/ritonavir (LPV/r) Kaletra® Aluvia®	Oral solution (Kaletra®) 80 mg Lopinavir (LPV) & 20 mg ritonavir (RTV) per ml Kaletra® capsules 133 mg LPV/33 mg RTV Aluvia® tablets 200 mg LPV/50 mg RTV Aluvia® half-dose (HD) tablets* 100 mg LPV/25 mg RTV	300 mg/m^2/dose LPV component (max. 400 mg LPV = adolescent dose)	2	Capsules should be refrigerated Oral solution should be refrigerated until dispensed Can be kept at room temperature up to 25°C if used within 6 weeks Aluvia tabs can be stored at room temperature	Aluvia® tabs can be given with or without food. Aluvia tabs **must** be swallowed whole Crushing the tabs reduces the absorption of the drugs Kaletra Solution and Capsules: administer with food. High-fat meal increases absorption, especially of the liquid preparation If co-administered with buffered ddI, ddI should be given 1 hour before or 2 hours after lopinavir/ritonavir Aluvia® can be taken with EC didanosine on an empty stomach Dose adjustments required if LPV/r used in combination with NNRTIs Kaletra® Capsules are being discontinued

progesterone-only oral contraceptives, while NNRTIs can be used. A combined oral contraceptive containing at least 30 µg of ethinyl oestradiol should be used. Progesterone-only injectables can be used with all ARVs. Concomitant consistent condom use is recommended for preventing HIV transmission

TABLE V. DOSAGE AND FREQUENCY OF ARVs IN CHILDREN (CONTINUED)

Drug	Formulations	Dosage (per dose)	Frequency	Storage	Comments
		Protease inhibitors (PIs)			
Ritonavir (RTV) Norvir®	Susp: 80 mg/ml Capsules: 100 mg	**No longer recommended for use as full-dose single PI** >1 mo.: 350 - 450 mg/m²/dose For pharmacological boosting of other PIs: see individual PI concerned **Boosting dose of RTV when used with rifampicin and LPV/r:** same dose in mg as LPV. Alternatively ¾ (volume) of Kaletra dose	2 2 2		Take with food Bitter: coat mouth with peanut butter or give with chocolate milk. Take 2 hours apart from didanosine Can be taken together with EC didanosine
Saquinavir (SQV) Invirase® – hard gel capsule	Hard gel capsules (HGC) 200 mg (only use together with RTV)	SQV 50 mg/kg RTV 100 mg/m² Adolescent /adult SQV 1 000 mg RTV 100 mg	2 2 2 2		Should always be used with RTV boosting Administer within 2 hours of a full meal to increase absorption Sun exposure can cause photosensitivity reactions; sunscreen or protective clothing recommended

*Awaiting MCC approval. Available with Section 21 authorisation.
Body surface area (m^2) = $\sqrt{(\text{height (cm)} \times \text{weight (kg)} \div 3\,600)}$.

and to compensate for any possible reduction in the effectiveness of the hormonal contraceptive.

- LPV/r co-administration can increase tenofovir levels by 30%, and may result in increased renal and bone toxicity.

The following website may be of assistance in assessing potential interactions:

http://www.hiv-druginteractions.org/frames.asp?drug/drg_main.asp

8. ADDITIONAL PRACTICAL POINTS

8.1 PRACTICAL DOSING

Although paediatric dosages are calculated using the child's weight or surface area, one must consider the practicalities of the dose. For example, 1.75 ml is very difficult to measure accurately, so a more practical dose is 2 ml (generally round upwards). Certain ARV solutions, e.g. LPV/RTV (Kaletra) or RTV (Norvir) are highly concentrated, so dosages do need to be calculated to the nearest 1/10th of a ml (but it is not necessary to calculate to the nearest 1/100th of a ml). Others, e.g AZT, 3TC, NVP (Viramune) or ABC (Ziagen) solutions, can quite safely be rounded up to the nearest ml. The volume of 3TC and ABC should always be the same, which makes dosing easier for caregivers. When using d4T capsules dissolved in water, dosages can be rounded up to the nearest 5 mg. Every effort should be made to switch to tablets or capsules as soon as possible. Certain drugs should still rather be dosed according to surface area, but where this is difficult the weight-based chart (Fig. 1) can be used.

Kivexa

Kivexa is a fixed-dose combination tablet containing 300 mg 3TC and 600 mg ABC. It is dosed as 1 tablet once a day and can be given to children >25 kg who can swallow this large tablet. It is particularly useful in older children to facilitate adherence.

Atazanavir (Reyataz)

ATV is a useful PI. It has the advantage of minimal lipid disturbances (although RTV boosting will cause some elevations of cholesterol and triglycerides). It should generally always be given with RTV boosting. Its advantages include once-daily dosing, a low pill burden and a good safety and tolerability profile. For this reason ATV may be a preferable alternative to Aluvia in PI-naïve older children in the private sector with adherence issues. It is best not to use ATV in PI-experienced patients unless one knows that no or limited PI mutations are present.

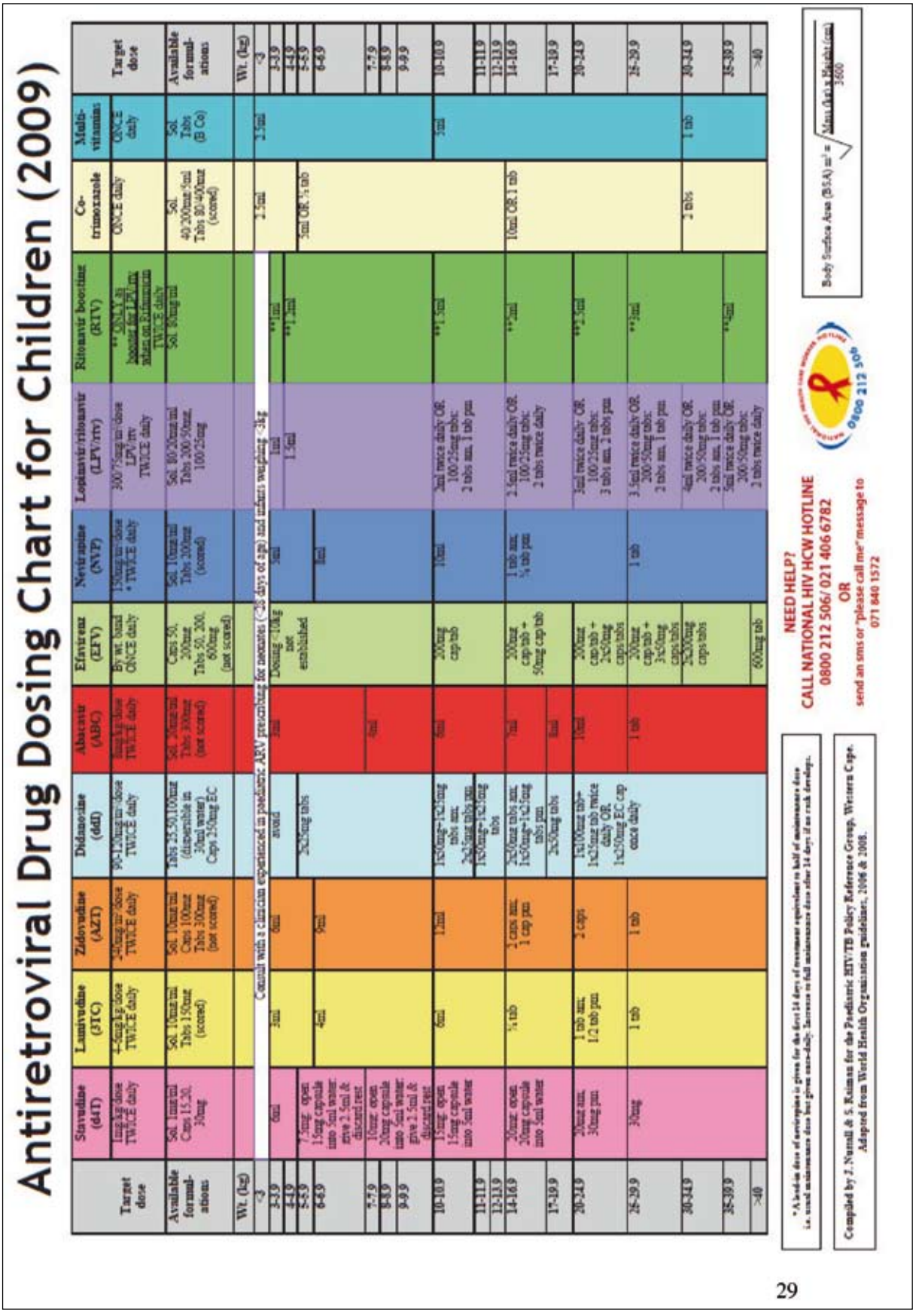

Fig. 1. Weight-based dosing chart.

8.2 TIMING OF DOSING

There is a common misconception that ARVs need to be given exactly 12 hours or 24 hours apart. This is because older drugs with very short half-lives needed to be dosed exactly on time. However, there is much more flexibility with the drugs in current use. Drugs with twice-daily doses can generally be given between 10 and 14 hours apart. For drugs that are dosed with meals, the best approach is to give them strictly twice daily with breakfast and supper. It is clearly much more important to fit the drugs into our patients' lifestyles than vice versa.

8.3 HAART AFTER FAILED MTCT PROPHYLAXIS

- **Where nevirapine was used as a single dose in prevention of mother-to-child (PMTCT) prophylaxis.** In the HIVNET 012 study, up to 45% of HIV-infected infants had NNRTI-associated resistance mutations after 1 dose of NVP to the mother and the infant. There are good data in adults and infants suggesting reduced efficacy of future NNRTI-containing highly active antiretroviral therapy (HAART) regimens. Results from P1060 also indicate that in children who have been exposed to NNRTIs for PMTCT, there is an increased risk of virological failure when NVP is used subsequently for treatment.[6] It is therefore advisable to avoid nevirapine and efavirenz as part of first-line therapy in this situation.
- **If AZT monotherapy was used in MTCT prophylaxis.** Data support its use in combination therapy for infected infants. Resistance has, however, been described.
- **If the mother was on triple combination therapy.** In this situation, do genotyping on the baby and design a regimen accordingly. If unable to do genotyping, avoid the drugs the mother was taking, especially if she had a detectable VL. If the mother had an undetectable VL, it is probably acceptable to use the same agents in her HIV-infected baby.

8.4 TUBERCULOSIS TREATMENT AND HAART IN CO-INFECTED CHILDREN

Rifampicin increases the breakdown of PIs and NNRTIs. Also, there are overlapping toxicities between TB drugs and ARVs. The immune reconstitution inflammatory syndrome (IRIS) causes morbidity and higher risk of mortality. IRIS can be misinterpreted as progression of TB or medication side-effects. In addition, the increased pill burden can impact on adherence.

Options

When to start ARVs:

- Since TB is a clinical stage 3 disease, most children will need to be started on ART. ART should be initiated 2 - 4 weeks after starting TB treatment. This may reduce the likelihood of immune reconstitution disease and will allow time to identify early adverse events from anti-TB drugs.
- If the CD4 count is normal and the child is >12 months old, initiation of ART may be delayed until completion of TB treatment. (Allow 2 weeks for the effects of rifampicin on the liver to 'wash out'.)
- If the child is already on ART when TB is diagnosed, continue ART with TB treatment. Monitor for IRIS and adapt ARVs as required.

What regimen to use:

- Try to make a bacteriological diagnosis. Submit all sputa and gastric washings for mycobacterial culture. All isolates require speciation into *Mycobacterium tuberculosis* and *M. bovis*-BCG and drug susceptibility testing. Make every effort to exclude multidrug-resistant (MDR) TB in the patient and in the source case.
- Use standard TB treatment (i.e. a rifampicin-based regimen).
- ARV regimens:

  >3 years: 2 NRTIs + efavirenz (standard dose)

  <3 years: 2 NRTIs + superboosted LPV/RTV 300 mg/m^2/dose bd + extra ritonavir (dosed at 0.75 × volume of LPV/r) bd to achieve per mg equivalence for LPV and RTV).

If RTV is not available, one can consider giving LPV/r 600 mg/m^2/dose bd. However, one should revert to superboosted LPV/RTV when RTV becomes available. The efficacy and toxic side-effects of this approach are unknown. Recent pharmacokinetic data show that super-boosted LPV/r yields good levels of LPV whereas simply doubling the dose yields suboptimal levels.[7]

8.5 SPECIFIC ISSUES FOR ADOLESCENTS

These issues apply to both vertically and sexually transmitted HIV.

- Non-adherence is often a problem, and strategies should be introduced to promote adherence, including more frequent visits and intensive counselling.
- Adult supervision of treatment should continue throughout adolescence and includes verification that the medicine has been swallowed.
- Disclosure of HIV status must have occurred before onset of sexual activity.
- Adolescent-friendly services include:
  - A specific convenient day set aside for adolescent clinics
  - Adolescent groups and peer support groups
  - Access to family planning, sexually transmitted infection (STI) treatment, cervical cancer prevention and screening and gynaecological services
  - Human papillomavirus vaccination.

8.6 CHANGING THERAPY

For toxicity or intolerance, a simple substitution can be made, being mindful of previous therapies that may have failed. Do not reduce dosage unless the reduced dose is still in the therapeutic range.

For failure of a regimen, proceed as outlined below.

Failure of first-line therapy

If viraemia occurs, even at a low level, check and encourage adherence. Also check dosages or other 'technical problems'. These include vomiting or spitting out medications and not receiving meds on time.

If the VL is persistently >5 000 copies/ml on two or three occasions despite good adherence and technical problems having been resolved, consider changing regimens. Be sure to resolve the adherence problems before changing therapy, otherwise the second regimen will fail. On the other hand, continuing with a failing regimen results in ongoing viral replication with the development of new mutations and cross-resistance, thus limiting future options.

Resolving adherence issues is paramount for any child failing ART. In children on a PI-based first-line regimen, adherence interventions may be sufficient. On the other hand, failing an NNRTI-based regimen invariably requires a regimen change after resolving adherence issues. See below for choice of second-line regimen.

Since virological failure usually precedes immunological and clinical failure, by changing on virological criteria, one can hopefully prevent clinical and immunological deterioration.

When failure is due to viral resistance, at least two new active drugs should be used. Previous drug history and genotyping (see below) are helpful in deciding on a new regimen.

In the case of NNRTI resistance

- There is no place for maintaining patients failing an NNRTI regimen on the same regimen; the longer it is maintained, the more resistance mutations are likely to occur.
- The regimen should be changed to a boosted PI with 2 active NRTIs (based on genotyping if possible).

In the case of PI resistance

- Patients on a boosted PI regimen not suppressing may have no PI and minimal NRTI mutations, in which case the original regimen may be resumed after addressing the adherence issues.
- In NNRTI-naïve patients with no NNRTI and at least 2 fully active NRTIs on genotyping, a simple switch to 2 NRTIs + NNRTI may be appropriate.
- Patients with multiple PI mutations may achieve viral control when some of the newer agents not yet registered in South Africa are used. Consult an expert.

Failure of second-line or subsequent regimens

In this situation, consult an expert.

8.7 RESISTANCE

Nucleoside analogues

Resistance is slow to develop, except for 3TC. Resistance to 3TC occurs within weeks on a non-suppressive regimen. Useful benefits of 3TC resistance are the partial reversal of AZT, d4T and TDF resistance and rendering HIV less pathogenic (M184V mutation).

Non-nucleoside reverse transcriptase inhibitors

There is complete cross-resistance between the currently available NNRTIs. A patient resistant to NVP will also have resistance to efavirenz (despite what the genotyping indicates). This does not apply to the new second-generation NNRTI (not yet available in South Africa) etravirine, which needs a few NNRTI mutations for high-level resistance. For this reason, a patient failing an NNRTI should change regimens soon to prevent compromising this future option.

Protease inhibitors

The boosted PIs are very slow to develop resistance and need several mutations before high-level resistance occurs. In a PI-naïve patient who fails a boosted PI, it is generally accepted that resistance mutations do not occur over a short period of time. However, if a patient has PI mutations from previous PI failure, new mutations can occur even with a boosted PI.

Resistance testing

At present only genotypic resistance testing is available in South Africa. Genotyping is still expensive (±R4 400). Genotyping will only provide information about resistance to the current regimen, and not necessarily about previous ART the child may have been exposed to. For this reason genotyping needs to be interpreted in conjunction with a detailed ART history. The interpretation is complicated and should be done in conjunction with an expert. Ideally genotyping should be done in any child whose VL is persistently above 5 000 copies/ml despite good adherence. Genotyping is also indicated for infants infected despite maternal HAART, before starting ART. Contact the South African HIV Clinicians Society for further information on when to perform and interpreting genotyping.

8.8 CHOICE OF SECOND-LINE REGIMEN

Patient failing ABC/3TC/EFV or d4T/3TC/EFV

Second-line choice: AZT + ddI + LPV/r. Genotyping, if available, may suggest an easier alternative regimen. Discuss with an expert.

Patient failing ABC/3TC/LPV/r or d4T/3TC/LPV/r

Current NDoH guidelines recommend AZT + ddI + NVP (<3 years) or EFV (>3 years). Some experts feel that this regimen is prone to failure. It is advisable to do resistance testing and /or discuss with an expert to devise a suitable second-line regimen.

After changing regimens, there should be frequent adherence and toxicity checks.

8.9 SWITCHING FROM A PI- TO AN NNRTI-CONTAINING REGIMEN

Numerous adult studies and one paediatric study have demonstrated the feasibility of switching from a PI to an NNRTI once VLs are <50 copies/ml. This approach will avoid some long-term adverse effects of the PIs. Only consider if VLs are consistently <50 copies/ml and adherence is excellent. Where the mother and/or baby were given a single dose of NVP for PMTCT, switching should be avoided until further data are available.

8.10 INTERRUPTING THERAPY

Generally ART should not be stopped except on the advice of an expert. When it is necessary to stop or interrupt a regimen containing an NNRTI, be aware that the long half-life of the NNRTI will cause sub-therapeutic levels to persist for up to several weeks. Either continue the NRTIs for a week after stopping the NNRTI if feasible (for example if NNRTI-associated rash is suspected) or use a boosted PI for a week to avoid developing resistance to the NNRTI.

8.11 IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

IRIS is characterised by a paradoxical clinical deterioration after starting HAART. This results from rapid restoration of pathogen-specific immunity to opportunistic infections (OIs) and causes deterioration of an existing infection (paradoxical IRIS) or new clinical manifestations of a previously unrecognised subclinical infection (unmasking IRIS) during the early stages of ART. IRIS is usually associated with improvements in surrogate markers of HIV infection (virological, immunological, clinical). It may have distinct clinical presentations with pronounced inflammatory response. IRIS usually occurs within 6 months of starting HAART and in patients with a low starting CD4 count. The most common presentations in South African children include BCG adenitis, TB and herpes zoster.

Causes include *M. tuberculosis,* BCG, *M. avium* complex (MAC), *M. leprae*, *Cryptococcus neoformans, Aspergillus, Candida albicans, P. jirovecii*, cytomegalovirus (CMV), JC virus, human herpesviruses, herpes simplex virus, varicella zoster virus, human papillomavirus and hepatitis B and C viruses (HBV, HCV).

9. SELECTED ADVERSE EFFECTS OF ANTIRETROVIRAL DRUGS IN CHILDREN (TABLE VI)

ARVs are generally well tolerated in children. A few more serious adverse effects are mentioned here.

9.1 LACTIC ACIDOSIS

Lactic acidosis is a rare but serious, life-threatening complication of NRTI therapy, especially when ddI and d4T are used together. Symptoms include nausea and vomiting, abdominal pain, tachypnoea and dyspnoea, weight loss and fatigue. It may also cause neurological symptoms including a Guillain-Barré-like picture. There is no value in screening for lactic acidosis in asymptomatic children. Clinicians should be aware of the symptoms and diagnose the condition timeously. Diagnosis is confirmed with a serum lactate level >5 mmol/l, metabolic acidosis and a raised anion gap. Liver enzymes may be increased.

In patients with a lactate level >10 mmol/l or >5 mmol/l with metabolic acidosis, ART should be discontinued and supportive therapy instituted. Treatment (usually in an ICU) consists of intravenous fluids and ensuring oxygenation. Some reports suggest that alkalinising the blood with bicarbonate might improve prognosis, but this remains controversial. Other controversial treatments include thiamine (vitamin B_1), riboflavin (vitamin B_2) and L-carnitine (no data to show efficacy).

Following an episode of lactic acidosis, it may take several months for lactate levels and liver enzymes to normalise. Contact the HIV Clinicians Society for assistance in designing a new regimen after lactic acidosis.

9.2 HAEMATOLOGICAL TOXICITY

The two major agents are AZT and co-trimoxazole (usually only high-dose co-trimoxazole for treating PCP, but occasionally with prophylactic doses, and this is reversible with folinic acid – not folic acid).

Patients on AZT should have full blood counts (FBCs) monitored monthly for the first 3 months and 3-monthly thereafter. The main bone marrow toxicities from AZT are anaemia and neutropenia.

Anaemia may be due to HIV infection itself, or to AIDS-related conditions such as disseminated MAC, CMV or lymphoma. It may also be nutritional (e.g. iron or folate deficiency) or drug-related. Management depends on the underlying cause of anaemia, available options and the extent of the problem. It is reasonable to switch to a drug that causes fewer haematological side-effects,

TABLE VI. ADVERSE EFFECTS OF ARVs IN CHILDREN*

Class	Drug	Adverse effects
NRTIs	AZT (Retrovir®)	Anaemia, granulocytopenia, myopathy, lactic acidosis
	ddI (Videx®)	Common: abdominal pain, nausea and vomiting Uncommon: diarrhoea, pancreatitis, peripheral neuropathy, lactic acidosis
	Stavudine (Zerit®)	Common: headache, rash, gastro-intestinal, lipo-atrophy Uncommon: pancreatitis, peripheral neuropathy (adults), lactic acidosis
	Abacavir (Ziagen®)	Hypersensitivity reaction (with or without rash) – fever, rash, fatigue, nausea, vomiting, diarrhoea, pharyngitis, dyspnoea, cough Elevated ALT, creatinine or CK. Lymphopenia Lactic acidosis
	Lamivudine (3TC®)	Well tolerated. Common: headache, fatigue and abdominal pain Uncommon: lactic acidosis
NtRTIs	Tenofovir (Viread®)	More common: nausea, diarrhoea, vomiting, flatulence Less common: osteomalacia, renal toxicity, lactic acidosis
NNRTIs	Nevirapine (Viramune®)	Skin rash, sedative effect and diarrhoea. Liver toxicity
	Efavirenz (Stocrin®)	Skin rash. CNS – sleep disturbance, confusion, abnormal thinking Teratogenic in primates, but prospective data in humans are reassuring (no higher than background fetal malformation rate). May be implicated in breast enlargement (lipomastia)
PIs	Ritonavir (Norvir®)	Nausea, vomiting, diarrhoea. Hypercholesterolaemia and hypertriglyceridaemia, lipodystrophy
	Atazanavir (Reyataz®)	Common: unconjugated hyperbilirubinaemia – usually mild and does not warrant discontinuing drug. Has less effect on lipids than other PIs but RTV boosting may affect lipids
	Lopinavir/ritonavir (Kaletra®)(Aluvia®)	Nausea, vomiting, diarrhoea. Hypercholesterolaemia and hypertriglyceridaemia, lipodystrophy
	Fosamprenavir (Telzir®)	Nausea, vomiting, diarrhoea. Hypercholesterolaemia and hypertriglyceridaemia, lipodystrophy. Less common (more severe): life-threatening rash, including Stevens-Johnson syndrome, in <1% of patients, neutropenia, elevated serum creatinine kinase levels
	Saquinavir (Invirase®)	Nausea, vomiting, diarrhoea. Hypercholesterolaemia and hypertriglyceridaemia, lipodystrophy

ALT = alanine transaminase; CK = creatine kinase.
*See section 9.

e.g. switch from ZDV to d4T or ABC. A haemoglobin level below 7 – 8 g/dl warrants investigation and treatment. Nutritional deficiencies, especially iron, should be addressed.

Neutropenia is quite common before or on HAART. Unless severe, $<0.25\times10^9$/l, neutropenia often resolves spontaneously (providing there are no associated signs such as persistent fever or localised infection) and a repeat FBC should be done a week later. If neutropenia is severe, $<0.25\times10^9$/l, the offending agent should be replaced if feasible.

9.3 RASHES

Most rashes following ARVs are mild to moderate and resolve spontaneously with drug continuation. Most rashes are either maculopapular or urticarial. The most severe rashes include Stevens-Johnson syndrome, toxic epidermal necrolysis, ABC hypersensitivity, and the drug rash with eosinophilia and systemic symptoms (DRESS) reported with NNRTIs.

The highest prevalence of drug rashes occurs with the NNRTIs (more severe and more frequent with NVP). Rash usually occurs in the first 2 - 4 weeks of treatment. The rash is usually maculopapular and erythematous.

NVP is given daily for the first 2 weeks and only increased to twice daily once the rash has resolved. Mild to moderate rashes will often resolve spontaneously but must be closely monitored. Oral antihistamines can be used in mild to moderate cases.

In children who develop severe rash, cutaneous bullae or target lesions, mucosal lesions or systemic symptoms, NVP

should be permanently discontinued and hospitalisation is required.

If NVP is discontinued for mild or moderate rash, restarting NVP after the rash has resolved may be considered with close monitoring.

Cross-reactivity among NNRTIs may occur. Therefore avoid EFV after a severe rash. However, in children with mild or moderate rash without mucosal involvement or systemic symptoms, EFV may be substituted with caution.

Rashes may occur in children receiving EFV. These rashes are usually less severe than those with NVP, and resolution during treatment continuation is common. However, if EFV-associated rash is severe, or is accompanied by mucosal or systemic symptoms, EFV should be permanently discontinued.

9.4 HYPERSENSITIVITY SYNDROME

ABC and NVP are most commonly implicated.

ABC hypersensitivity reaction occurs in 4 - 8% of patients but is less common in black Africans. There is a 100% correlation between skin patch test-positive reactions and HLA B*5701. HLA B*5701 is rare in black Africans. Hypersensitivity reaction *usually* occurs in the first 6 weeks of ABC. ABC hypersensitivity is multisystemic. Fever and rash occur commonly and may be associated with nausea, vomiting, diarrhoea, fatigue, myalgia and arthralgia. Respiratory symptoms, such as pharyngitis, cough or dyspnoea, may also be present.

The skin rash, usually maculopapular or urticarial, occurs in about 70% of cases. Symptoms worsen with each dose. ABC hypersensitivity reaction is fully reversible on discontinuing ABC, and fatalities have not been reported on first exposure to the drug. Patients must however *never* be rechallenged with ABC after a hypersensitivity reaction, as deaths have occurred due to hypotension. Parents need specific counselling to recognise the hypersensitivity reaction; they also require a letter to alert any health care worker who may be consulted and need the contact number of the prescribing doctor.

A hypersensitivity reaction has been described for NVP. Systemic symptoms such as fever, myalgia, arthralgia, hepatitis, and eosinophilia may occur. It usually occurs in the first 8 weeks of treatment. NVP should then be permanently discontinued and EFV should be avoided as well.

9.5 HEPATOTOXICITY

All three classes of ARV drugs currently in use in South Africa have been implicated. Liver dysfunction in HIV infection may be caused by HIV, co-infection with hepatitis B or C viruses, OIs, malignancies, drug interactions or drug-induced hepatotoxicity. NRTI-associated hepatotoxicity is primarily caused by mitochondrial toxicity. NNRTIs are associated with asymptomatic elevations in liver enzymes and hypersensitivity with hepatitis. NVP is associated with more hepatotoxicity than EFV. PI-associated elevations in liver enzymes can occur at any time during therapy. Patients with chronic hepatitis B or C may experience an increase in liver enzymes after starting HAART as part of IRIS. There may also be an increase in liver enzymes after discontinuing drugs such as 3TC or TDF (which are used to treat hepatitis B). Children do seem to get less hepatic dysfunction on HAART than adults.

Patients on NVP should have liver function tests (LFTs) done 2-weekly for the first 2 months, then 3-monthly thereafter. LFTs should be monitored routinely 3 - 4-monthly in patients on other HAART regimens.

If transaminases are elevated <10 times the upper limit of normal (ULN) there is no need to interrupt HAART. Patients with clinical hepatitis or severe hepatotoxicity (>10 × ULN) should have a work-up for other causes of hepatitis, e.g. hepatitis A, B or C, and interruption of HAART. Patients on NVP with clinical hepatitis should discontinue NVP and have their HAART regimen changed. Rechallenge with NVP or ABC after acute hepatitis is not recommended. Patients with hepatitis B co-infection may need to continue with 3TC if their HAART regimen is changed to prevent a flare-up in hepatitis B.

9.6 LIPODYSTROPHY (LIPO-HYPERTROPHY/LIPO-ATROPHY)

Lipodystrophy typically involves accumulation of visceral fat in the abdomen (central obesity), dorso-cervical area (buffalo hump) and breasts (visceral fat accumulation) and/or loss of subcutaneous fat in the face, extremities and buttocks (lipo-atrophy (LA)). PIs have been implicated in fat accumulation, whereas the NRTIs, especially stavudine, have been implicated in LA. EFV may be implicated in breast enlargement. There are no data in children, but adult data suggest that switching from d4T or ZDV to ABC will at least arrest and may partially reverse LA but not the visceral fat accumulation. Switching early, when the LA is mild, is advisable as LA may be irreversible. There are also limited data indicating that switching to a regimen containing a PI and an NNRTI only will also reverse LA.

9.7 HYPERLIPIDAEMIA

PIs (especially RTV and LPV/r) are implicated in hyperlipidaemia. However, both d4T and EFV have also been implicated. While PI therapy in adults is associated with an increased risk of cardiovascular disease, there is currently no evidence of an association between elevated cholesterol levels in children and an increased risk of premature death. As a result, there is no consensus

or experience in lipid-lowering agents in children. Cholesterol and triglycerides should be measured 12-monthly in children on PIs. A random cholesterol and triglyceride is probably adequate, but if these are raised, a fasting level should be done. Referral to a dietician and encouraging exercise are the first interventions. If these are unsuccessful, consult the HIV Clinicians Society. Options available include observation, ARV agent switching (e.g. from a PI to an NNRTI or to ATV), or lipid-lowering agents. Statins are metabolised by cytochrome P450 resulting in either toxicity or diminished effect with RTV, so use with caution and only on the advice of an expert.

10. PROPHYLAXIS

10.1 *PNEUMOCYSTIS JIROVECII* PNEUMONIA

Indications for co-trimoxazole prophylaxis and when to start and stop it are set out in Table VII.

Re-institute co-trimoxazole prophylaxis if the CD4 count or percentage subsequently drops and the criteria in Table VII for starting prophylaxis are reached.

10.2 INH PROPHYLAXIS

The following children should receive INH prophylaxis:

- HIV-infected infants and children with a positive PPD test (>5 mm)
- HIV-infected infants and children exposed to a person who has contagious TB.

Active TB disease first needs to be excluded. The dosage of INH is 10 - 15 mg/kg/day and it should be continued for 6 months. Where the source case has INH-resistant TB, give rifampicin 15 mg/kg/d for 4 - 6 months. For MDR and extensively drug-resistant (XDR) contacts an expert should be consulted.

TABLE VII. CO-TRIMOXAZOLE PROPHYLAXIS

Indications for co-trimoxazole	When to start	When to stop
All HIV-exposed newborns	Start from 4 - 6 weeks after birth	Stop when PCR negative ≥6 weeks after full weaning AND infant is clinically HIV negative
All HIV-exposed exclusive formula-feeding children (EFF)	Start from 4 - 6 weeks after birth	Stop when PCR negative AND infant is clinically HIV negative AND EFF is expected to continue
All HIV-exposed breastfeeding children	Start from 4 - 6 weeks after birth	Stop when PCR negative ≥6 weeks after full weaning AND infant is clinically HIV negative
HIV-infected infants <12 months old	Start from 4 - 6 weeks after birth or as soon as possible after HIV diagnosis even if on HAART *Note:* all HIV-positive infants <1 year should be started on HAART regard-less of clinical stage or CD4 count or percentage	All infants <12 months should remain on prophylaxis
HIV-infected children 1 - 5 years with or without ART	All symptomatic children (WHO clinical stage 2, 3 or 4) or CD4 <15% or <500 cells/µl*	Stop once ART-associated immune recon-stitution has occurred for ≥6 months, i.e. CD4+ percentage ≥15% or CD4 count ≥500 cells/µl on ≥2 occasions, 3 - 6 months apart
HIV-infected children ≥6 years of age with or without HAART	Start if CD4 count <200 cells/µl or <15% OR WHO clinical stage 3 or 4 disease (including TB)	Stop once ART-associated immune recon-stitution has occurred for ≥6 months: CD4 ≥15% or ≥200 cells/µl on ≥2 occasions, 3 - 6 months apart
Any HIV-infected child with high risk for bacterial infections, e.g. severe malnutrition, on oncological drugs or corticosteroids or at risk of malaria	Start co-trimoxazole prophylaxis even with ART immune reconstitution	Do not stop until risk has been eliminated and all CD4 cell percentage or CD4 cell count criteria listed above have been met
HIV-infected child with previous PCP infection	Start as soon as first PCP episode has been treated	Stop once ART-associated immune recon-stitution has occurred for ≥6 months in children over 1 year of age: CD4 ≥15% or ≥500 cells/µl (1 - 5 years) or ≥200 cells/µl (>6 years) on ≥2 occasions, 3 - 6 months apart

**Note:* any one of the criteria could be used for starting therapy.

10.3 *MYCOBACTERIUM AVIUM* COMPLEX

MAC is a true OI. Disseminated MAC only occurs in patients with extremely low CD4 counts, although it is unusual in very young children. The best prophylaxis against MAC is ART and immune recovery. Where resources allow, there is a role for azithromycin prophylaxis against disseminated MAC in patients with extremely low CD4 counts. Before prophylaxis is instituted a mycobacterial blood culture should be done to exclude disseminated MAC. Children aged 2 - 5 years with a CD4 count <75 cells/µl and >6 years with a CD4 count <50 should be offered azithromycin prophylaxis. The dosage of azithromycin is 20 mg/kg body weight (max. 1 200 mg) orally once weekly. Discontinue once the CD4 count has been >200 cells/µl for children aged 2 - 5 years and >100 cells/µl for children aged ≥6 years for >6 months in children on stable ART.

Disclaimer: Specific recommendations provided in this document are intended only as a guide to clinical therapy, based on expert consensus and best current evidence.

Recommended drugs and dosages are based on current available data and may differ from dosages recommended by manufacturers. Treatment decisions for patients should be made by their responsible clinicians with due consideration for individual circumstances. The most current version of this document should always be consulted.

RECOMMENDED READING

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 23, 2009; pp 1-139. http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf

Sharland M, Castelli G, Ramos JT, Blanche S. Gibb DM. On behalf of the PENTA Steering Committee Penta Guidelines for the use of Antiretroviral Therapy in Paediatric HIV Infection. www.ctu.mrc.ac.uk/PENTA/

WHO guidelines: www.who.int

NDoH guidelines: www.doh.gov.za/

Centers for Disease Control and Prevention. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-Exposed and HIV-Infected. *MMWR Morb Mortal Wkly Rep* 2009; 58 (No. RR-11): 1-166.

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7. McIlleron H, Ren Y, Nuttall J, *et al.* Double-dose lopinavir/ritonavir provides insufficient lopinavir exposure in children receiving rifampicin-based anti-TB treatment. Presented at the 16th Conference on Retrovirology and Opportunistic Infections, 8 - 11 February 2009, Montreal.

CLINICAL

WHEN TO START ANTIRETROVIRAL THERAPY IN INFANTS AND CHILDREN

Mark F Cotton, *FCPaed (SA), PhD, DTM&H, DCH (SA), Cert ID (SA)*
Helena Rabie, *FCPaed (SA), MMed (Paed)*
Department of Paediatrics and Child Health and KID-CRU, Tygerberg Children's Hospital and Faculty of Health Sciences, Stellenbosch University, Tygerberg, W Cape
Ute Feucht, *FCPaed (SA), MMed (Paed), Dip HIV Man (SA), CAHM*
Department of Paediatrics, Kalafong Hospital and University of Pretoria
Avy Violari, *FCPaed (SA)*
Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, Soweto, Johannesburg

We review the background and key studies that inform decisions on when to initiate antiretroviral therapy (ART) in infants and children. The World Health Organization staging system from 2006 was based on conditions commonly seen in Africa and provided an impetus for advancing ART in children. Because of poor predictive value of CD4 counts in infancy and inability to predict risk of death or disease progression, we recommend initiating ART in all infants under a year of age. CD4 thresholds for initiating therapy decline as children become older. WHO stage 3 and 4 should trigger ART regardless of CD4 count. Over 5 years of age, a CD4 count <350/µl requires ART.

When to initiate antiretroviral therapy (ART) in children and adults has been determined by disease stage and CD4 count or percentage. The starting criteria were based on cohort data and clinical experience. The main groups determining paediatric guidelines are from the USA, Europe (PENTA - Paediatric European Network for Treatment of AIDS) and the World Health Organization (WHO).[1-3] With the advent of effective triple therapy from 1995, guidelines have adapted to new data. Initial staging clinical and immunological criteria were those of the Centers for Diseases Control and Prevention (CDC).[4] The staging criteria were based on North American experience and were not always appropriate for Africa. For example, failure to thrive, bronchiectasis and pulmonary tuberculosis were not adequately addressed.

Although the CDC classification included CD4 depletion, it was only with the HIV Prognostic Markers Collaborative Study (HPMCS), representing the combined data of 3 941 HIV-infected infants and children from the USA and Europe in the pre-highly active antiretroviral therapy (HAART) era, that the relationship between age and CD4 percentage became clearer.[5] The study showed that the younger the infant, the higher the CD4 percentage or absolute count at which there was a high risk of disease progression or death within the next 12 months. As the CD4 count normally declines with age until 5 years of age and the CD4 percentage remains stable, the CD4 percentage is used as a guideline until then (in the absence of lymphopenia). However, the CD4 count is an extremely accurate predictor of outcome.[6] These findings were subsequently incorporated into all paediatric guidelines.

The establishment of a WHO classification system in 2006 helped to focus on conditions more frequently encountered in Africa.[7] The system has 4 stages, with ART recommended for stages 3 and 4. The special vulnerability of young infants to rapid disease progression and death was not fully appreciated at this time, although allowance was made for initiating ART in HIV antibody-positive infants with severe disease before confirmation by HIV DNA polymerase chain reaction (PCR).

The decision on when to initiate ART in infants and children has always been influenced by fears of long-term toxicity or antiretroviral (ARV) resistance if therapy is started too soon. Also, ARV choices for children are far more limited than for adults. Second-line therapy is especially unsatisfactory.

However, there is increasing realisation, especially from adult data, that delaying ART until the CD4 cell count falls below 350 cells/µl is associated with increased morbidity and mortality.[8,9] ART is therefore recommended at higher CD4 thresholds than previously.

INFANTS BELOW 12 MONTHS OF AGE

Mortality in HIV-infected infants is exceedingly high. The first data came from a study of combined outcome in nine vertical transmission prevention (VTP) studies conducted in sub-Saharan Africa.[10] Thirty-five per cent of HIV-infected infants had died by 1 year of age and 52.5% by 2 years of age. The ZVITAMBO study in Zimbabwe showed a similar but slightly higher mortality in the first 2 years of life.[11] For both studies, co-tri-

moxazole prophylaxis for prevention of *Pneumocystis* pneumonia (PCP) was not given.

The Children with HIV Early Antiretroviral (CHER) trial is the first ARV trial to prospectively evaluate ART strategies to inform ARV guidelines.[12] Before this, limited cohort studies favoured early ART. For example, Faye *et al.* reported an improved outcome in 40 infants commencing ART before 6 months of age compared with 43 starting later. In the early group there was no disease progression versus 7 events, including 3 cases of encephalopathy, in those treated later.[13]

CHER commenced in July 2005 in two South African sites, the Perinatal HIV Research Unit (PHRU) in Soweto and the Children's Infectious Diseases Clinical Research Unit (KID-CRU) at Tygerberg in the Western Cape. The hypothesis of the study is that early ART will have long-term benefit by delaying the need for continuous therapy. At the time of planning and initiation, the standard practice in infants was to initiate ART for a low CD4 percentage (<20% until August 2006 and 25% thereafter, in the first year of life) or evidence of severe clinical disease.[3,14] In the first part of the study, infants with baseline CD4 ≥25% were randomised to deferred ART (arm 1), where ART was initiated once treatment criteria were reached (CD4 <20% until August 2006 and <25% thereafter or severe HIV disease), or early ART commencing before 12 weeks of age until either the first (arm 2) or second (arm 3) birthdays, with interruption of ART until indicated through CD4 depletion (<20% after the first birthday) or clinical disease progression. For the first year of the study, deferred ART (arm 1) was compared with early ART (arms 2 and 3).

On 20 June 2007, after the study had been open for 2 years, the Data Safety Monitoring Board for CHER, noting significantly improved survival in subjects in the early ART arms, recommended that no infants be randomised to deferred ART and that data until this time point be released.[12] The difference in mortality and disease progression is shown in Fig. 1.

A key finding in CHER was high early mortality, mainly in the deferred arm, which diminished as the infants became older (Table I). Also of note, however, is that mortality was also higher early on in the early ART group, diminishing over time in the first year of the study.

Subsequently, ARV guidelines for children throughout the world incorporated the findings of CHER and recommended that all HIV-infected children below 12 months of age start ART irrespective of CD4 status or disease progression.[1, 2,15]

More recently, a study by Bourne and colleagues, using birth and death data from Statistics South Africa between 1997 and 2002, showed a peak in post-neonatal

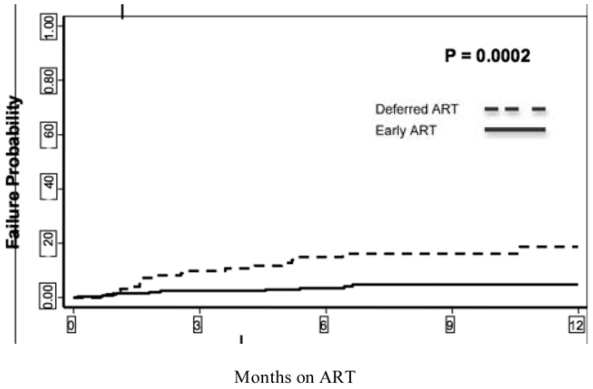

Fig. 1. Deferred ART is associated with a) a higher probability of death or b) first HIV event in the CHER trial.

TABLE I. HIGH EARLY MORTALITY RATE IN THE CHER STUDY

Weeks on study*	Death rate per 100 person-years (95% CI) Early ART	Deferred ART
0 - 13	9.8 (3.6 - 21.4)	40.6 (21 - 71)
>13 - 26	3.7 (0.4 - 13.2)	19.7 (6.4 - 45.9)
>26 - 52	3.1 (0.4 - 11.2)	6.8 (0.8 - 24.7)

*Infants were ≤12 weeks of age at study entry.[12]

mortality, rising each year directly proportional to the rising HIV antenatal seroprevalence.[16] These data are shown in Fig. 2. Also of note is that neonatal deaths are not addressed. It is possible that HIV may contribute significantly to neonatal deaths as well.

These data, together with CHER, illustrate the enormous dilemma and problems for child health programmes. In CHER the diagnostic HIV DNA PCR was done from 4 weeks of age with a 7-day turnaround time. In the public sector, the PCR is done at 6 weeks of age, to coincide with the 6-week immunisation visit. Turnaround time for the test results and then communication to the caregiver all take time during a period of great vulnerability.

One of the main problems is identifying HIV-infected children early and getting them into care. Because of

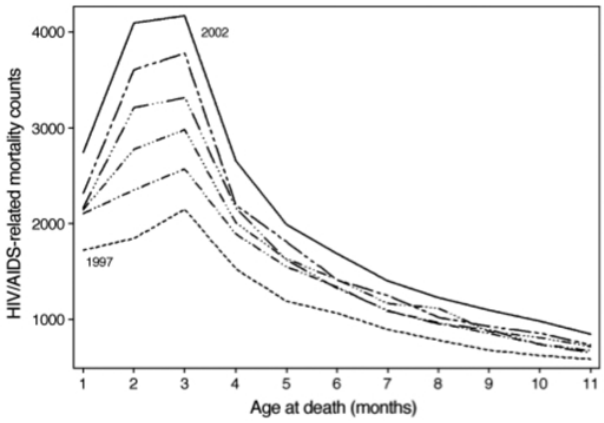

Fig. 2. Early peak in infant mortality proportional to rising antenatal HIV seroprevalence, 1997 - 2002 (reproduced with permission from AIDS[16]*).*

the importance of the caregiver in giving ARVs, previous guidelines emphasised adequate preparation and training over a number of weeks. Because of the new recognition of early infancy as a period of high mortality, there is a need to 'fast-track' preparation and also to continue training and support after having initiated ARVs.

Practical difficulties are illustrated by experience in the Tshwane district. In 2009, 82% of children newly referred to the Kalafong ART site had stage 3 or 4 disease, the majority being referred from the in- and outpatient service. Of the 14 000 - 22 000 HIV-infected children thought to be in Tshwane, only between 3 000 and 4 000 are receiving ART or are in care.

CHILDREN >12 MONTHS OF AGE

In this group there is less certainty on when to initiate ART. Ideally, decisions must be based on randomised studies. The PREDICT is underway in Thailand and Cambodia and will assess the CD4 thresholds for therapy in children between 1 and 12 years of age.

All guidelines recommend using absolute CD4 counts from 5 years of age. For simplicity, the WHO regards 1 - 5 years of age as a single group, while the PENTA guidelines have 1 - 3 and 3 - 5 years of age. This group of children also represents a wide age spectrum. Clinical disease stage is extremely important and the majority of children are symptomatic. The dissociation of CD4 from disease severity has been well documented in South African children.[17] The HPMCS data, although showing a low risk of disease progression for higher CD4 percentages, still showed notable death and disease progression with CD4 >30% up to 6 years of age.[5,6]

Initial data suggested that young children show excellent immune restoration once ART is initiated, but more recent studies suggest a poorer response if therapy is delayed to CD4 <15%. Initial reports also suggested that viral suppression was difficult to achieve, especially in younger infants with extremely high viral loads. However, potent regimens and a better understanding of pharmacokinetics have improved outcomes.

Importantly, health care providers caring for children often do not fully appreciate the extent of end-organ damage. Mild cognitive and behavioural changes, milder forms of chronic lung disease, renal and hepatic disease and poor growth may easily be overlooked, leading to irreversible organ damage, growth failure and delayed puberty.

In the 3C4KIDS, 2 510 children over a year of age from Africa and Brazil contributed 357 deaths and 3 769 child-years at risk.[18] None had access to ART, with 81% follow-up occurring on co-trimoxazole. The 12-month risk of death was higher than in the HPMCS for CD4 count and percentage. Most importantly, when anaemia and failure to thrive were included, the CD4 thresholds for predicting death or severe disease were much higher (Fig. 3). Both of these conditions are markers for advanced HIV disease. Most importantly, there was a real risk of death at high CD4 counts and percentages. For these reasons, our guidelines favour earlier ART between 1 and 5 years of age, in keeping with current US recommendations.[2]

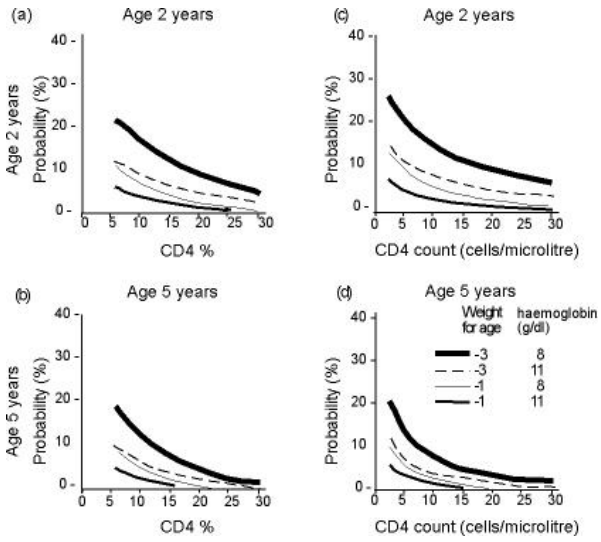

Fig. 3. Estimated risk of death within 12 months for a child on co-trimoxazole prophylaxis by age, weight-for-age z-score and haemoglobin and CD4 percentage or count. (a) CD4% at 2 years of age; (b) CD4% at 5 years of age; (c) CD4 count at 2 years of age; and (d) CD4 count at 5 years of age (reproduced with permission from AIDS[18]).

CONCLUSION

There has been much progress in refining and improving ARV guidelines for children. More changes can be expected as knowledge advances. Most important, however, is the realisation that each child is unique and his or her individual and family circumstances need to be considered for maximum benefit.

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PHARMACOKINETICS OF ANTIRETROVIRAL DRUGS IN INFANCY

Helen McIlleron, *MB ChB, PhD*
Division of Clinical Pharmacology, Department of Medicine, University of Cape Town
Hermien Gous, *PharmD*
Harriet Shezi Children's Clinic, Enhancing Children's HIV Outcomes (ECHO), Chris Hani Baragwanath Hospital, Johannesburg

Dosing in infancy is complicated by inadequate characterisation of pharmacokinetics, unpredictable drug concentrations and a lack of suitable dosage forms. Additional challenges are presented by the concomitant administration of interacting drugs (e.g. rifampicin in antituberculosis treatment) and disease conditions that may alter drug disposition. The extent and implications of breastmilk transfer of drugs to the infant are poorly understood. New technologies facilitate pharmacokinetic studies in infants and will improve access to therapeutic drug monitoring.

Infancy (from birth until 1 year of age) is a time of rapid changes in the body of a child. These changes affect pharmacokinetics in many ways. The CHER study[1] showed that early antiretroviral (ARV) treatment reduces mortality and disease progression among infants acquiring HIV infection before 12 weeks of age. As a result the World Health Organization has recently revised treatment initiation recommendations in children less than 1 year of age: all infants under 12 months of age with confirmed HIV infection should be started on ARV therapy, irrespective of clinical or immunological stage.[2] Dosing in infants is challenging because drug concentrations are highly variable, there is frequently scant pharmacokinetic information on young children, and few suitable drug formulations are available. Furthermore, adherence to treatment is reliant on the caregiver rather than the patient. Peri- and postnatal HIV transmission are reduced by maternal highly active ARV treatment (HAART). However, the benefits and risks to breast-fed infants of exposure to maternal ARV drugs during lactation are poorly understood.

In this article we review the pharmacokinetics of ARV drugs relevant to South African infants, and highlight some of the challenges to delivering ARV treatment in safe and effective doses.

PHARMACOKINETIC PRINCIPLES

Growth and development are accompanied by changes that influence drug concentrations. As these developmental changes begin *in utero*, post-conceptional age is a better descriptor of maturation than postnatal age. Size and age explain a considerable part of the pharmacokinetic variability. However, there is a non-linear relationship between clearance and size. Consequently, simple proportional adjustment of the adult dose based on weight leads to underestimation of the maintenance dose required in children. Dose calculation methods based on scaling of clearance do not account for changes during early infancy in multiple processes affecting drug absorption, distribution, metabolism and elimination. In recent years there has been a trend to provide simplified dosing guidelines using weight bands, which provide many practical advantages. Ideally dosing would also account for differences in lean body size and maturity within the weight bands.

Drug absorption is highly variable and difficult to predict. It is determined by multiple interacting factors including enteric pH, gastric motility, intestinal transit time, the physico-chemical properties of the drug, intestinal metabolic capacity and activity of drug transporters. Gastric pH rapidly declines and then rises again during the first few days of life. Acidity then increases over several months, reaching adult levels (pH 2 - 3) between 2 and 7 years. Frequent feeding with milk or formula may influence gastric pH. The absorption of atazanavir is reduced at a higher pH and it should be taken with food to enhance bio-availability. Although by 36 weeks' gestational age an infant has developed intestinal motility patterns similar to those in adults, motility is irregular and variable, and the frequency of movement is reduced until 6 - 8 months of age. Dietary factors affect the rate of gastric emptying: increased caloric density feeds with increased concentrations of complex fat and sugars delay gastric emptying, so formula-fed infants may have shorter intestinal transit times than breast-fed infants.[3]

Body composition changes affect drug distribution. Total body water (TBW) comprises approximately 90% and 75% of body weight in preterm and term infants, respectively. By 1 year of age TBW approaches adult proportions of 60%. Extracellular fluid ranges from 65% in premature to 40% in term infants, while adult

values of 20% are reached after a year. Preterm infants have very little body fat (1 - 5%). Term infants typically have 12 - 15% body fat. By 12 months body fat increases to approximately 30% before declining to adult levels of 18%.

Tissue binding of drugs also affects their distribution. Bound drugs are inactive. Free drug concentration (unbound drug) gives a better indication of how much drug is available for distribution to the site of action. In adults, lopinavir is highly bound to plasma proteins (98 - 99%), mainly α_1-acid glycoprotein (AAG), for which it has the higher affinity, and albumin. Several other protease inhibitors (PIs) are highly bound to plasma proteins. Marked changes in plasma protein concentrations and their binding characteristics occur during the first 2 weeks after birth. Albumin, which binds acidic and neutral drugs, increases by almost 30% in the first week. Basic drugs bind to AAG, globulins and lipoproteins. Neonates have AAG concentrations one-third those of children aged 1 year and older. The lower pH of neonatal blood (7.25 - 7.3) results in an increased free fraction of some drugs. Moreover, drugs may compete with free fatty acids and unconjugated bilirubin for binding sites. The increased permeability of the blood-brain barrier during infancy may have implications for those with HIV-related encephalopathy.

PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) undergo extensive pre-systemic (in the intestine and liver) and systemic (largely hepatic) metabolism. The cytochrome P450 (CYP) enzymes CYP 3A4 (PIs and nevirapine) and CYP2B6 (NNRTIs) are important isoforms for ARV biotransformation. Unlike most nucleoside reverse transcriptase inhibitors (NRTIs), zidovudine and abacavir are extensively metabolised in the liver: both drugs by glucuronidation, and abacavir by the enzyme alcohol dehydrogenase. Maturation of drug metabolising enzymes accounts for age-associated differences in metabolism. Differential rates of maturation are associated with the specific metabolic enzymes. Activity of CYP 3A4 in the fetus is 30 - 70% of that in adults. CYP activity increases during infancy. By 1 year of age the activity of most CYP isoforms exceeds adult values. The capacity for glucuronidation is limited at birth and highly variable. Adult levels of activity are achieved between 2 months and 3 years of age.

The activity and expression of drug transporters such as p-glycoprotein are important determinants of drug absorption, distribution and clearance. Very little is known about the developmental pattern of these transporters which, like those of the drug metabolising enzymes, may be influenced by exogenous factors such as diet in addition to genetic and maturational determinants.

NRTIs other than zidovudine and abacavir are eliminated primarily unchanged by the kidneys. Both glomerular filtration and tubular secretion are immature at birth. Before 34 weeks' gestation the glomerular filtration rate (GFR) is reduced and highly variable. Thereafter, there is a strong correlation between GFR and age. Term infants have a GFR of 2 - 4 ml/min, which increases to 8 - 20 ml/min during the first few days of life. In contrast, premature infants may be born with a GFR of 0.6 - 0.8 ml/min, which may increase to 2 - 4 ml/min during the first few days after birth. By 3 - 6 months of age adult maturity in GFR is attained.[3]

There are frequently inadequate pharmacokinetic data on infants. Moreover, studies in infants are often limited by small sample size and sparse sampling. Table I sets out pharmacokinetic data for ARV drugs used in South African infants.

DOSAGE FORMS

Dosing of infants is challenging. They cannot swallow solid dosing forms. Liquid formulations often have decreased stability and require refrigeration. Stavudine, for example, comes in a powder that needs reconstitution before dispensing as an oral solution. It is stable for only 30 days in a refrigerator. Lopinavir/ritonavir solution may be stored at room temperature (up to 25°C) if it is used within 42 days. In many high-burden settings access to refrigeration is limited. Stability issues therefore complicate drug supply, storage and dispensing. Most tablets and capsules should not be crushed, as stability and absorption may be altered and accurate dosing is impossible. Dispensing and dosing errors are common, as the dose has to be translated into the volume dispensed or administered. Accurate measurement of the dose is challenging for many carers, and liquid formulations need to be shaken well before administration to ensure that the correct dose is administered. Relatively large-volume liquid doses can be problematic: infants do not always swallow the entire dose and often spit some of it out. Paediatric formulations such as dispersible fixed-dose combination tablets in doses suitable for infants and young children may provide considerable advantages.

THERAPEUTIC DRUG MONITORING

The routine use of therapeutic drug monitoring (TDM) has not been proven to alter treatment outcomes in adults. However, it is recommended that TDM be considered in paediatric patients (particularly infants and severely ill children) owing to unpredictable drug exposure and, in many instances, a paucity of evidence to support the dosing guidelines. Additional indications include potentially significant drug-drug (see 'Impact of antituberculosis treatment', below) or drug-food interactions; gastro-intestinal disease, or hepatic or renal

TABLE I. TARGET CONCENTRATIONS, AVERAGE CONCENTRATIONS IN ADULTS ON STANDARD ANTIRETROVIRAL DOSES AND PHARMACOKINETIC DATA FOR ANTIRETROVIRAL DRUGS USED IN SOUTH AFRICAN INFANTS

Drug (active ingredient/s)	Recommended dose in infants[11]	Recommended target concentration*	Average Pk in adult	Pk data in infants/ young children	Comments	References
Protease inhibitors						
Lopinavir (LPV)/ritonavir (co-formulated in a 4:1 ratio; Kaletra oral solution)	**14 days - 6 months:** 300 mg LPV/ m2 BSA 12-hourly, or 16 mg LPV/kg 12-hourly >6 months: 230 mg LPV/m^2, 12 mg LPV/kg if <15 kg, or 10 mg LPV/kg if ≥15 kg. Doses given 12-hourly	Lopinavir C_{min} >1.0 mg/l	C_{min} 5 - 8 mg/l	**<8 weeks:** Median LPV C_{min} 2.22 mg/l (9 infants aged 5.6 - 7.9 weeks; median dose 276 mg/m^2) **6 weeks - 6 months:** C_{min} 2.37 mg/l (18 infants 1.6 - 5.9 months old; average dose 267 mg/m^2). In both studies PK sampling was 2 weeks after starting treatment. As C_{min} increased at later times, difficulties with dose administration may in part account for low concentrations **>6 months:** Median C_{min} 4.64 mg/l (15 South African children 9 - 47 months; median LPV dose 269 mg/m^2)	Once-daily dosing is NOT recommended. No data in combination with anti-TB treatment, NNRTIs or other PIs in <6-month-olds. AUC in children >6 months dosed with 230 mg LPV/m^2 approximates that in adults, although C_{min} is lower	4 - 6
Ritonavir (RTV)	**> 1month:** 350 - 450 mg/m^2 BSA 12-hourly	C_{min} >2.1 mg/l	C_{min} 4 mg/l	4 weeks - 24 months: C_{min} was low and highly variable among 35 infants: RTV 350 mg/m^2 twice daily and 450 mg/m^2 twice daily resulted in median C_{min} of 0.99 mg/l and 0.74 mg/l, respectively	Not recommended in infants ≤1 month old; doses of 450 mg/m^2 12-hourly resulted in low plasma concentrations. Low RTV concentrations are linked to inferior viral responses in children	7, 8
Indinavir (IDV)	Not approved for use in children	C_{min} >0.1 mg/l C_{max} <10.0 mg/l	IDV alone: C_{min} 0.1 - 0.4 mg/l; IDV/r: C_{min} 0.2 - 0.5 mg/l	3 month- to 16-year-olds given IDV 50 mg/kg (±600 mg/m^2) 8-hourly achieved C_{min} median (range) 0.07 mg/l (0.02 - 0.21). CL/F was higher in <6-year-olds (2.5 v. 1.0 l/h/kg) and more variable. IDV 400 mg/m^2 plus 100 - 125 mg/m^2 ritonavir 12-hourly achieves satisfactory IDV concentrations in older children	Should not be used in neonates owing to the risk of kernicterus. A safe and effective dose has not been established in children. Dose-related nephrolithiasis is a concern	9 - 11

TABLE I. CONTINUED

Drug (active ingredient/s)	Recommended dose in infants[11]	Recommended target concentration*	Average Pk in adult	Pk data in infants/ young children	Comments	References
Protease inhibitors						
Nelfinavir (NFV)	Not approved for use in <2-year-olds	C_{min} >0.8 mg/l	C_{min} 1.5 mg/l	NFV 45 mg/kg twice daily from birth: median C_{min} 3.2 mg/l on day 7, but by day 14 and 28 only 0.7 mg/l. Similarly, <6-week-olds on 40 mg/kg twice daily achieved median C_{min} 1.35 mg/l with 3 of 11 infants failing to reach AUC targets. Older infants may require even higher doses: 50% of 2.3 - 8.5-month-olds on an average 136 mg NFV/kg/d failed to reach the AUC target	Doses of NFV 25 - 35 mg/kg 3 times a day, or 45 - 55 mg/kg twice daily, are used in children 2 - 13 years, but younger children require higher doses	12 - 14
Atazanavir (ATV)	Not approved for use in children <6 years of age	C_{min} >0.15 mg/l	ATZ 400 mg/d: C_{min} 0.27 mg/l; ATZ/RTV 300/100 mg/d: C_{min} 0.86 mg/l	The recently reported results of NIH PACTG study P1020A demonstrated adequate ATV concentrations (C_{min} 0.43 mg/l; AUC_{0-24} 48.54 mg/h/l) in 3 - 24-month-olds using RTV boosted ATV 339 mg/m². CL/F was high in infants (12.4 l/h/m^2 with median age 0.8 years v. 2.9 l/h/m^2 with median age 10.5 years)	Avoid in <3-month-olds: risk of kernicterus. RTV-boosting achieves higher C_{min} with lower C_{max}, and inter-individual variability is reduced. Higher mg/m^2 doses are required in children compared with adults: the recommended daily dose in infants >3 months old is ATV/RTV 310/100 mg/m^2	15,16
Non-nucleoside reverse transcriptase inhibitors						
Nevirapine (NVP) for PMTCT	**Perinatal:** 200 mg single maternal dose during labour + single dose of 2 mg/kg to infant up to 72 h after birth	C_{min} >0.1 mg/l (10 × *in vitro* IC_{50})	-	Transplacental transfer after a single maternal 200 mg dose during labour maintains infant NVP >0.1 mg/l for several days. A 2 mg/kg NVP dose at 48 - 72 h keeps NVP >0.1 mg/l for a week in most infants (0.11 - 0.28 mg/l in 7-day-old infants). A study evaluating chronic NVP (4 mg/kg from birth to 14 days, then 8 mg/kg until 24 weeks) for breast-feeding infants found NVP >0.1 mg/l in 95% and 100% of those receiving twice weekly or daily doses; once-weekly dosing was insufficient in >60% of infants	Evaluation of chronic NVP administration (4 mg/kg/d) for prevention of breastmilk transmission is ongoing. Long-term maternal NVP before delivery accelerates NVP elimination in newborns, presumably due to *in utero* autoinduction of NVP elimination	17 - 19

TABLE I. CONTINUED

Drug (active ingredient/s)	Recommended dose in infants[11]	Recommended target concentration*	Average Pk in adult	Pk data in infants/ young children	Comments	References
Non-nucleoside reverse transcriptase inhibitors						
Nevirapine	**>14 days:** 150 - 200 mg/m^2 BSA once daily for 14 days then twice daily	C_{min} >3.0 mg/l	C_{min} 4 - 6 mg/l	Zambian infants (mean age 5.3 months) had mean NVP AUC_{0-12h}, C_{max} and C_{min} of 78.7 h/mg/l, 8.1 mg/l, and 4.9 mg/l, respectively. Three of 6 infants <5 months old (receiving NVP 324 - 406 mg/m^2/day, in 2 doses), had subtherapeutic C_{min}	NVP absorption is variable and delayed. Elimination is prolonged in newborns, but accelerates during the first days of life; infants require higher mg/m^2 doses than older children	20
Nucleoside reverse transcriptase inhibitors						
Lamivudine	**<30 days:** 2 mg/kg twice a day **≥30 days:** 4 mg/kg twice daily	-	CL/F 0.3 l/h/kg; $t_{1/2}$ 6 h; IC $t_{1/2}$ (of active triphosphate) 15 h	**Infants 3 - 28 days old:** mean CL/F 0.37 l/h/kg; AUC_{0-12} 6.0 mg/h/l on 2 mg/kg twice daily. In contrast, infants >1 month had mean CL/F 0.66 l/h/kg; 4 mg/kg twice daily achieved mean AUC 6.8 mg/h/l	Excreted unchanged in the urine. CL/F doubles during the first month, after which it stabilises for the duration of infancy	21
Zidovudine (ZDV) for PMTCT and premature infants	**<2 weeks:** 2 mg/kg/12 h (IV: 1.5 mg/kg) **2 - 6 weeks:** increase to 8-hourly			CL/F is low in premature neonates (0.15 l/h/kg). In term newborns CL/F is 0.34 l/h/kg before increasing rapidly to 0.65 l/h/kg by 7 days and 1.14 l/h/kg in infants >14 days old		22
Zidovudine	**<6 weeks:** 2 mg/kg/6 h (IV: 1.5 mg/kg) **≥6 weeks:** 4 - <9 kg: 12 mg/kg/12 h; **≥9 kg:** 9 mg/kg/12 h	-	CL/F 1.5 l/h/kg; $t_{1/2}$ 1.1 h		1st-pass metabolism reduces bioavailability by 35%. Undergoes hepatic glucuronidation; a small amount is excreted unchanged in urine	
Stavudine	**0 - 13 days:** 0.5 mg/kg 12-hourly **>13 days:** 1 mg/kg 12-hourly	-	CL/F 35.6 l/h; $t_{1/2}$ 1 h; IC $t_{1/2}$ 3.5 - 7.0 h	CL/F 5.6 ml/min/kg at 1 week, 6.8 ml/min/kg at 6 weeks. On 1 mg/kg/12 h, 14- and 28-day-olds had similar AUC (1.9 mg/h/l) and $t_{1/2}$ (1.1 - 1.2 h)	Absorption is delayed in neonates	23
Didanosine	**2 weeks - 8 months:** 100 mg/m^2 12-hourly **>8 months:** 120 mg/m^2 12-hourly	-	CL/F 1 l/h/kg; $t_{1/2}$ 1.5 h; IC $t_{1/2}$ 12 - 40 h	Although variable, one study found little change in CL/F between the 1st day of life and 6 weeks (CL/F 4.5 and 5.0 l/min/m^2 respectively). Other sources report CL/F to be 4-fold higher in 6-week-olds than in newborns	50 mg/m^2 12-hourly is recommended in newborns. Unstable at low pH (hence given with antacid)	23

TABLE I. CONTINUED

Drug (active ingredient/s)	Recommended dose in infants[11]	Recommended target concentration*	Average Pk in adult	Pk data in infants/ young children	Comments	References
Non-nucleoside reverse transcriptase inhibitors						
Abacavir	**≥3 months:** 8 mg/kg twice daily	-	300 mg^2 × day and 600 mg daily: AUC_{0-24} 8 mg/h/l	Single 8 mg/kg dose in 3 - 23-month-olds: mean AUC 8.67 mg/h/l. There are few data in infants receiving repeated doses, but the drug's pharmacokinetic properties are similar across age groups	Not approved for use in <3-month-olds. Clearance is increased in children; the recommended 8 mg/kg dose is double the adult mg/kg dose	24

*Concentration-based cut-off values for performing TDM of antiretroviral agents in naïve patients.[25]
Pk = pharmacokinetic; PMTCT = prevention of mother-to-child transmission; BSA = body surface area; IV = intravenous; IC = intracellular; AUC = area under the concentration-time curve; CL/F = apparent clearance; C_{max} = peak concentration; C_{min} = trough/minimum concentration; IC_{50} = 50% inhibitory concentration; $t_{1/2}$ = half life.
Fosamprenavir is not approved for use in infants but is currently being evaluated in South African children 1 - 6 months old.

impairment; treatment-experienced patients who may have viral isolates with reduced susceptibility to highly active ARV therapy (HAART); use of alternative dosing regimens the safety and efficacy of which have not been established in clinical trials; concentration-dependent toxicity; unexpectedly poor virological response in a treatment-naïve person; and monitoring of adherence.[25]

The minimum (predose trough) drug concentration is used to monitor virological efficacy. Peak concentrations relate more closely to toxicity for some drugs, and the area under the drug concentration-time curve is a measure of overall systemic exposure. Therapeutic ranges have not been defined for NRTIs, which are metabolised intracellularly to the active triphosphate, as plasma concentrations are not closely related to efficacy.

Target concentrations for NNRTIs and PIs (Table I) are based largely on studies in adults. While it is likely that good responses to treatment will be achieved in children, provided that they are given drug formulations and doses that achieve drug exposure similar to those that have demonstrated safety and efficacy among adults, important differences may apply. Routinely, total plasma ARV concentrations are measured in the laboratory. The recommended drug concentration ranges are therefore based on the sum of the free active component and protein-bound drug. Altered protein binding during early infancy may alter the proportion of active drug in the measured concentration. Furthermore, day-to-day variability complicates interpretation of a single drug concentration result. Drug concentration results should be interpreted on an individual basis, and safety and efficacy should also be carefully monitored. Clearly, poor adherence to treatment needs to be ruled out as a cause of low drug concentrations before dose adjustments are made.

Modern technologies such as liquid chromatography mass spectrometry allow drug concentration measurement in low-volume samples, thus facilitating TDM in infants. The development of methods using blood spots dried onto filter paper is likely to make TDM increasingly accessible and affordable. However, although it is frequently indicated in infants as part of an integrated approach, TDM of ARVs is currently not available to the vast majority patients in high-burden settings.

IMPACT OF ANTITUBERCULOSIS TREATMENT

Although the use of ARV therapy complicates the management of tuberculosis, patients with tuberculosis who meet the criteria for ARV therapy should be started on an effective ARV regimen once they are established on rifampicin-based antituberculosis treatment.

Through activation of the pregnane X receptor, which results in increased expression of multiple drug metabolising enzymes and transporters, rifampicin increases the oral clearance of many medications. Rifampicin lowers the concentrations of PIs to subtherapeutic levels; nevirapine trough concentrations are reduced by about 30% in South African adults;[26] and zidovudine concentrations are reported to decline by 50%. There are concerns associated with all the currently available co-treatment options for infants, and there are very few data on which to base optimal co-treatment approaches. Careful monitoring is indicated.

In HIV-infected infants exposed to single-dose nevirapine, or maternal NNRTI-containing ARV treatment or prevention regimens, PI-based HAART should be started. Super-boosted lopinavir (extra ritonavir is added to lopinavir/ritonavir; a total 12-hourly lopinavir/ritonavir dose of 230/230 mg/m^2) achieves adequate lopinavir exposure in most children older than 6 months during rifampicin-containing antituberculosis treatment.[27] However, lopinavir concentrations are highly variable, there are no data to support this approach in younger infants, and it is poorly tolerated and complex to prescribe, dispense and administer. Double-dose lopinavir/ritonavir has been shown to result in sub-therapeutic concentrations in children during antituberculosis treatment. When adjusted doses of PIs are used with rifampicin, TDM should be implemented if it is available, and it is essential to regularly monitor liver function. Rifabutin (in reduced doses) is preferred to rifampicin in adults requiring PIs, but it is expensive and suitable formulations are not available for infants and young children.

In many settings nevirapine plus 2 NRTIs is the only effective treatment option available to young children. Standard doses of nevirapine twice daily provide acceptable outcomes in adults with tuberculosis (although it is inferior to efavirenz). Recent evidence suggests, however, that the majority of young children on tuberculosis treatment fail to achieve trough concentrations >3 mg/l (the lower limit of the recommended range),[28] and data for infants younger than 6 months are lacking. The approach should be used with caution until more safety and efficacy information is available, and patients should be carefully monitored.

ARV regimens comprising 3 or 4 nucleos(t)ides have inferior efficacy compared with PI- and NNRTI-based regimens, and are not adequately evaluated in children. However, they may have a role in ARV-naïve patients with HIV-associated tuberculosis, as the substantial interactions of rifampicin with the PIs and NNRTIs are avoided.

ARVS IN BREASTMILK

The use of ARV drugs by mothers is increasing as access to treatment programmes improves, thresholds for starting treatment become less stringent and ARVs are implemented to prevent HIV transmission during childbirth and breastfeeding. However, the benefits and risks to breastfed infants of exposure to maternal ARV drugs during lactation are poorly understood. The different physicochemical properties of drugs lead to differential transfer from maternal plasma to breastmilk (Table II) and to the breastfed infant. Incomplete exposure of infants to components of a maternal regimen may favour the selection of drug-resistant virus should transmission occur. Little is known about the safety of ARVs in breastmilk. The small doses of NRTIs and PIs ingested through breastmilk may invoke subtle or idiosyncratic side-effects, while the more substantial exposure to nevirapine and efavirenz are of more importance.

A study of ARV concentrations in exclusively breastfed Kenyan infants younger than 6 months, whose mothers were receiving HAART, found biologically significant concentrations of lamivudine and nevirapine, but not zidovudine.[29] Lamivudine concentrations were just greater than the 50% inhibitory concentration (IC_{50}) for wild-type HIV. Median nevirapine concentrations (0.90 mg/l) were well above the median HIV IC_{50} (0.017 mg/l).[29] Rwandan infants of mothers receiving efavirenz-based HAART achieved median efavirenz concentrations of 0.87 mg/l through breastmilk ingestion, just below the recommended target trough concentration of >1 mg/l.[30] Transfer of NNRTIs from mothers receiving HAART may therefore result in substantial exposure in their breastfed infants along with potential benefit for prevention of HIV transmission, the risk of side-effects and the risk of developing viral resistance to NNRTIs

TABLE II. ANTIRETROVIRAL DISTRIBUTION TO BREASTMILK AND INFANT EXPOSURE RESULTING FROM MATERNAL HAART

Drug	Median breastmilk/maternal plasma ratio (IQR)	Estimated median daily infant dose from breastmilk	Median infant concentration	Reference
Zidovudine	0.44 (0.23, 0.65)	1.35 µg/kg/d (<1 000 × lower than standard infant dose for PMTCT)	Undetectable*	29
Lamivudine	2.56 (1.79, 3.89)	182 µg/kg (2% daily treatment dose for >3-month-olds)	0.02 - 0.03 mg/l*	29
Nevirapine	0.75 (0.64, 0.89)	600 µg/kg/d (15% of the 4 mg/kg/d infant dose being evaluated in PMTCT studies)	0.73 - 1.03 mg/l*	29
Efavirenz	0.52 (0.43, 0.62)	-	0.87 mg/l†	30
Lopinavir	0.11 (0.06, 0.15)	-	Undetectable†	31
Ritonavir	0.11 (0.08, 0.18)	-	Undetectable†	31

*Whole blood concentrations from 2 to 14 weeks after birth.
†Plasma concentrations 6 weeks to 6 months after birth.
IQR = intraquartile range; PMTCT = prevention of mother-to-child transmission.

should HIV transmission occur. Conversely, breastmilk concentrations of PIs are low and there is little if any transfer to the infant via breastmilk.[31]

CONCLUSION

The pharmacokinetics of infancy are unique and evolve rapidly during this period of life. Drug doses used during infancy are often based on extrapolation from other age groups. For many of the ARV drugs, evidence to support the dosing approaches is rudimentary and suitable dosage forms are lacking. It is important to ensure that adequate concentrations of ARV drugs are obtained, to ensure efficacy and prevent toxicity. The infant is further exposed to maternal ARV drugs before and during birth, and during lactation. There is an urgent need for pharmacokinetic studies in the relevant infant populations to support optimal dosing approaches which should then undergo more extensive evaluation of efficacy and safety. As drug concentrations in infants are highly unpredictable, particularly in neonates and premature infants, severely ill children or those treated concomitantly with interacting medications, TDM has a role in optimising individual dosing.

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WEIGHT-BAND DOSING TABLES: SIMPLIFYING PAEDIATRIC ART

James J C Nuttall, *MB ChB, DTM&H*
Paediatric Infectious Diseases Unit, Red Cross Children's Hospital and University of Cape Town

One of the obstacles to scaling up paediatric antiretroviral therapy (ART) coverage in resource-limited settings is the relative complexity of paediatric dosing. There is a need to simplify ART in order to facilitate treatment initiation and ongoing management of infants and children by health care providers, as well as to support adherence in the home. This article reviews the development of weight-band dosing tables as a strategy for simplifying the delivery of paediatric ART.

In 2007, only 8% of the estimated 1 800 000 children (0 - 14 years) living with HIV in sub-Saharan Africa were receiving antiretroviral therapy (ART). Coverage will need to be expanded greatly if the goal of providing ART to 80% of children in need by 2010 is to be met.[1] Moreover, recent evidence highlights early initiation of ART as particularly critical for infants with HIV.[2] Clinical guidelines issued by the World Health Organization (WHO) now recommend immediate initiation of ART for all HIV-infected infants.[3]

Paediatric ART management involves a complex process of interactions between patients, families, health care providers and the antiretrovirals (ARVs) themselves. Barriers to the delivery of effective treatment occur both within the health care system and in the home. These include delayed diagnosis, limited availability of health care providers trained in paediatric ART, few available paediatric ARV formulations, complicated regimens and dosing schedules, and poor palatability of some ARVs. Difficulties in the home include overcrowding, difficult work schedules of the parents and the stresses associated with parental disclosure in the home. Unlike adults, children require changes in antiretroviral dose as they grow and become older, and rely upon adult caregivers to administer medicines.[4]

Children have traditionally been dosed according to body surface area (BSA) (e.g. zidovudine (AZT), didanosine (ddI), lopinavir/ritonavir (LPV/r)), weight (mg/kg) (e.g. stavudine (d4T), lamivudine (3TC), abacavir (ABC), nevirapine (NVP)) or dose per weight band (efavirenz (EFV)). Manufacturers' recommendations for some ARV drugs (e.g. LPV/r) include both BSA and weight-based dosing methods.[5] The calculation of BSA generally requires accurate measurement of the child's weight and length or height (ideally with a stadiometer or measuring box), and a normogram or mathematical formula (e.g. Mosteller formula).[6] For both BSA and mg/kg weight-based dosing approaches, the calculated dose of each ARV drug must be rounded up or down as a 'best-fit' dosage according to which solid or liquid formulations of the ARV drug are available. This may lead to confusion and uncertainty on the part of the prescriber.

In resource-limited settings (RLS), primary care doctors and nurses rather than paediatricians are responsible for the majority of paediatric ART initiation and follow-up. Lack of accurate measuring equipment and the relative complexity of BSA dosing may inhibit initiation of ART in infants and young children or mean that inappropriate doses are given. While the most 'accurate' dosing may be obtained with the use of liquid formulations, large volumes of solutions (which may require refrigeration, e.g. d4T solution) may be challenging for caregivers to administer to young children, particularly if palatability is poor (e.g. LPV/r).

ART simplification strategies are required to help health care providers manage ART in children, and to help caregivers and children adhere to therapy. Interventions include the use of adult or preferably paediatric fixed-dose combinations (FDCs), selection of doses based on weight band rather than individual mg/kg or BSA doses, prescription of pills or capsules rather than liquids, and identification of reliable once-daily regimens.

MOVING FROM BSA AND WEIGHT-BASED DOSING APPROACHES TO WEIGHT-BAND DOSAGE TABLES

Weight-band dosage tables assist health care providers by assigning a fixed dose of medication for a particular weight range (e.g. 1.5 ml of LPV/r solution for children weighing 4 - 9.9 kg, or half a 150 mg 3TC tablet for children weighing 14 - 19.9 kg). In large public sector

treatment programmes, tables can reduce the time and risk of dosing errors involved in calculating multiple ARV doses by weight or BSA. They can also facilitate easier checking of doses against weight gain by clinicians, nurses, pharmacists or adherence counsellors. Under-dosing of ARVs, due in part to a lack of regular dose adjustments for ongoing growth, has been described in a large cohort of children in the UK and Ireland.[7] A study in Thailand found that 17 of 18 doctors using a standardised drug dosage table avoided miscalculations and reported more confidence with prescriptions.[8]

In 2006, the WHO published simplified weight-band dosing tables on all ARV drugs for which there were available paediatric indications, formulations or sufficient information and evidence to provide guidance on prescribing and doses.[9] Decisions about dosing were based upon manufacturers' information, ARV formulation choices, available data from clinical studies and expert paediatric pharmacology consultation. What was considered to be the 'optimal' dose for a particular weight band, given the limitations imposed by currently available drug formulations, was selected. Weight-band doses were determined by using BSA values calculated from median height-for-weight from international growth charts using the following formula: BSA = square root [[weight (kg) × height (cm)]/3 600].

The dosing tables are directed at RLS and are based on the following principles:

1. It is preferable to use one formulation or fixed combination of any given drug(s).
2. Syringes or other standardised devices of various sizes should be available to support accurate dosing of liquid formulations.
3. Large volumes of liquid or syrup formulations should be avoided where possible.
4. In general, children should be switched to available solid formulations as soon as possible or as soon as they are tolerated.
5. If liquids or syrups are difficult because of storage, large volumes required or palatability, solid dosage formulations are preferable.
6. If solid formulations of first-line and second-line drugs developed for children are unavailable, solid formulations currently used for adults can be used.
7. Many tablets, but not all, may be divided in half but not beyond as drug content cannot be guaranteed. Scored tablets are more easily split. Some tablets cannot be split, and the WHO recommends that where possible tablet splitting be done in the dispensing pharmacy using appropriate tablet cutters.
8. Some adult FDCs may result in under-dosing of individual components in children. This is of concern, particularly with drugs such as NNRTIs and 3TC where there is a low threshold for resistance. NVP requires a 'lead-in' dosage. During the first 2 weeks, therefore rather use individual components of the regimen.
9. Different dosing between a.m. and p.m. should be avoided where possible. However, in order to keep all regimens to no more than twice daily, there are instances where different quantities of solid dosage forms can be administered a.m. as opposed to p.m.
10. The doses in the tables are presented in weight bands, accepting that some deviation from target dosing will occur.
11. Children have to be weighed at each clinic visit, and dose changes are required as children grow and/or gain weight.
12. When capsules are opened or tablets dissolved or crushed and added to food or liquid, it is important that the entire volume/amount of vehicle be taken to ensure administration of the full dose.

The dosing tables are based on standardised weight bands starting from 5 kg body weight for the individual ARV drugs (excluding EFV, which starts from 10 kg) and 10 - 14 kg for the fixed-dose combinations (AZT + 3TC, d4T + 3TC, AZT + 3TC + ABC, d4T + 3TC + NVP). The weight bands are in 1 kg divisions from 5 to 11 kg, and 2 - 5 kg divisions from 12 to 35 or 40 kg.

ADAPTING WEIGHT-BAND DOSING TABLES FOR DIFFERENT SETTINGS

Dosing tables may be adapted according to the specific drug formulations available to a regional or national treatment programme. For example, dual (d4T + 3TC) or triple (d4T or AZT + 3TC + NVP) FDCs play an important role in paediatric ART in many countries (e.g. Thailand and many African countries), but are not widely used in South Africa. Satisfactory early clinical and immunological outcomes have been described following the use of fractions of generic adult FDCs in children dosed according to a weight-band table method in Thailand.[10]

In another project, a visual dosing aid (VDA) incorporating coloured dosing bands for five first-line ARV drugs was developed to assist clinicians in prescribing paediatric ART consisting of syrups, generic adult tablets or a combination. It compared well with generic paediatric FDC tablets and could help facilitate paediatric ART roll-out in RLS.[11]

The South African national guidelines for the management of HIV-infected children (2005) incorporate a weight-band dosing chart[12,13] developed by the Centers for Disease Control and Prevention (CDC) and a number of international paediatric AIDS programmes

prior to the more widespread availability of FDCs. BSA dosing recommendations were converted to weight-band doses using approximations of weight-for-age and height-for-age derived from standardised growth charts of girls from birth to 36 months and 20 years in the USA (National Center for Health Statistics). Dose for each weight band was based on the practicality of the available dosage forms for each drug, and practical storage and dosing instructions were included with the chart. The chart lacks dose recommendations for children weighing less than 5 - 7 kg and for HIV-TB co-infection.

The Western Cape Antiretroviral Drug Dosing Chart for Children (2007), based on the 2006 WHO recommendations, was developed by the author and colleagues as a pilot project for the HIV Directorate of the Western Cape (South Africa) provincial health department. The chart was directed at both clinicians and pharmacists involved in prescribing and dispensing ART for children, and it was successfully piloted at a number of HIV clinics before being distributed across the province. It was produced as a laminated A4 colour copy. Standard first- and second-line ART regimens (including regimens compatible with rifampicin-based TB treatment) as well as general comments relating to storage, administration and common drug interactions and side-effects of the individual ARV drugs were printed on the reverse side. Only ARV formulations available at public sector treatment facilities were included (no FDCs were available), and there was an emphasis on the early introduction of solid formulations where possible. Fractions of tablets (not less than half a tablet) were only incorporated for scored tablets. The target dose in mg/kg or mg/m^2 for each drug as well as the formula for calculating BSA was included to facilitate comparison of dosing methods when necessary.

The following local practices were incorporated:

1. The off-label 'opened capsule' d4T dosing method whereby a d4T capsule is opened and the powder contents dispersed in a standardised volume of water and the required dose drawn up with a syringe and administered to the child (e.g. to administer a standardised d4T dose of 10 mg for the weight bands 7 - 9.9 kg, a 20 mg d4T capsule is opened and dispersed into 5 ml of water and 2.5 ml is withdrawn with a syringe and administered and the remaining 2.5 ml is discarded). The rationale for this method is to minimise the use of stavudine solution (1 mg/ml when reconstituted), which is expensive, requires refrigeration, and results in relatively large medication volumes for administration to young infants at the usual dosing schedule (1 mg/kg/dose). There are now data based on high-performance liquid chromatography analysis of active drug concentration in dispersed capsule solutions, supporting the accuracy of this method for certain brands of d4T capsules.[14]
2. Standardised doses of ritonavir used for pharmacological boosting of LPV/r (in order to achieve a ratio of 1:1) in children receiving concurrent LPV/r and rifampicin-based TB treatment.[15]
3. Colour coding of ARVs on the chart corresponding to colour coding methods used in the pharmacy for medication containers and syringes to assist parents and caregivers with correct dosing.
4. The chart incorporated co-trimoxazole and multivitamin syrup dosing according to weight bands.
5. Since there were no standard weight-band dosing recommendations for infants weighing <5 kg in the WHO document (2006), it was recommended that a clinician experienced in ARV prescribing be consulted for such cases.

VALIDATION OF WEIGHT-BAND DOSING TABLES

There are a number of approaches to validation of weight-band dosing. Direct methods include pharmacokinetic (Pk) studies and therapeutic drug monitoring. Indirect methods include comparison of weight-based with BSA doses, and safety and efficacy studies. Qualitative studies assessing the usefulness of a weight-band dosing table to prescribing clinicians and dispensing pharmacists should be undertaken.

Differing growth rates and the prevalence of malnutrition could have a significant impact on the accuracy of weight-band dosing of drugs that are usually dosed by BSA. A study comparing the calculated BSA dose range with WHO weight-band doses for AZT, ddI, NVP and LPV/r using actual heights and weights of 601 children at the time of ARV initiation was undertaken at a tertiary hospital in South Africa in 2007.[16] The median age was 28 months (interquartile range 13 - 62), 49% of children weighed <10 kg, and 59% and 63% of children had weight-for-age and height-for-age z-scores ≤–2 (moderate to severe underweight or stunting), respectively. Children with body weight <5 kg were excluded as weight-based dosing recommendations were unavailable for this category, and children <6 months of age were excluded as LPV/r BSA dosing recommendations are different in this age group. The BSA dose ranges used were AZT 180 - 240 mg/m^2, ddI 90 - 120 mg/m^2, NVP 160 - 200 mg/m^2, and L/r 230 - 300 mg/m^2.

Results are presented in Table I. The conclusion of this study was that the 2006 WHO simplified weight band-dosing method effectively avoided under-dosing children in relation to existing BSA dose recommendations for AZT, NVP and LPV/r suspensions. However, the authors noted that the risk of over-dosing is greater with weight-band recommendations for existing capsule or tablet formulations of these ARVs. Further studies are recommended for the WHO weight-band dosing method.

TABLE I. WEIGHT-BAND DOSE RELATIVE TO CALCULATED BODY SURFACE AREA DOSE RANGE

ARV drug, BSA dose range, formulations assessed	Weight-band dose relative to calculated BSA dose range (*N*=601 children) (using anthropometric data at time of starting ART)	
	Under-dosing (% of children)	Over-dosing (% of children)
AZT		
180 - 240 mg/m^2		
Oral solution (10 mg/ml)	2	0.5
Capsules (100 mg)	8.5	19
ddI		
90 - 120 mg/m^2		
Tablets (25, 50, 100 mg, chewable or dispersable in water)	0	87
NVP		
160 - 200 mg/m^2		
Oral suspension (10 mg/ml)	0	53
Tablets (200 mg)	0	61
Lopinavir/ritonavir		
230 - 300 mg/m^2		
Oral solution (80/20 mg/ml)	1.2	26
Capsules (133.3/33.3 mg soft)	0	38

A VDA to facilitate dosing calculations in response to children's growth and weight during ARV treatment developed by Callens *et al.*[11] was evaluated using anthropometric data from 55 children from the USA and 324 children from the Democratic Republic of Congo (DRC). In comparison with WHO-recommended dosing, the authors noted a relative dosing difference of ≥20% in <3% of children for NVP, AZT and d4T but in 20% of children for 3TC, over-dosing being more frequent.[11]

A detailed review of Pk studies and clinical outcome, safety and efficacy studies undertaken in children treated with individual or FDC ARV drugs dosed according to weight bands is beyond the scope of this article. There are no reported Pk or clinical studies directly comparing weight band with mg/kg or BSA dosing approaches.

CURRENT WEIGHT-BAND TABLES

In July 2008, the WHO published a revised weight-band dosing table for individual ARVs as well as dual and triple FDCs applicable to children ≥6 weeks of age, indicating the number of tablets or millilitres of solution to be administered twice daily by weight band from 3 kg to 34.9 kg (Fig. 1).[17] The table focuses on ARVs used in first-line regimens and was developed by the WHO Paediatric Antiretroviral Working Group using the 2006 WHO treatment recommendations, target doses and weight bands as a benchmark and reviewing currently available published and unpublished data to assess dosing. DdI is not included in the dosing table. Key supporting references are provided in the document.[18] See Table II for target doses or dosing ranges.

A WHO generic tool was used to assess and evaluate the expected dose delivered of any product in relation to intended target doses. For all formulations, changes in the number of pills and switches from one formulation to another occur at the same weight bands. There was an attempt to avoid dosing any single ARV component below 90% of the intended delivered dose and not more than 25% above the intended dose (or dose range for products with an established dose range). For NVP, the aim was to avoid dosing below 100% of the minimum of the dose range (150 mg/m^2). Discrepancies between dose delivered and intended dose were justified based on available Pk data, consideration of toxicity, and threshold for development of HIV drug resistance. Higher dosing for children who would fall into the lower weight bands (under 3 years) was accepted for drugs with known increased metabolism or clearance in the young child (NVP, 3TC, d4T, abacavir, LPV/r).

In South Africa, the Antiretroviral Drug Dosing Chart (2009) is an update of the 2007 Western Cape version and incorporates elements of the WHO 2008 table; in particular, dosing recommendations for weight bands 3 - 3.9 kg and 4 - 4.9 kg (Fig. 2). Many of the formulations in the WHO table, in particular the FDCs, are not currently available to public sector treatment programmes in South Africa and so are excluded. The registration and availability of the paediatric strength heat-stable LPV/r tablet (Aluvia; 100 mg lopinavir/25 mg ritonavir) is still awaited, but it has been included. Local dosing practices described in the 2007 chart have been retained with modification, e.g. the d4T opened-capsule method is now used from 5 kg body weight. A comparative analysis of the revised weight band dosing in comparison with BSA dosing for AZT, NVP and L/r has been completed but not yet published. An analysis of the dose of LPV/r solution in mg/m^2 that revised WHO weight band dose recommendations would provide, using anthropometric data on 976 children initiating ART at median age of 11.2 months, indicated doses considerably in excess of 300/75 mg/m^2, particularly for children <6 months of age.[19] A protocol for an infant Pk study using the revised WHO weight-band dosing

Drug	Strength of tab (mg) or liquid mg/ml	Number of tablets or ml by weight band (twice daily)												Strength of adult tab (mg)	Number of tablets by weight band (twice daily)	
		Children 6 weeks of age and above (0.75 BD is delivered as 1 tablet AM and 0.5 tablets PM and 1.5 BD is delivered as 2 tablets AM and 1 tablet PM)														
		3-3.9 kg	4-4.9 kg	5-5.9 kg	6-6.9 kg	7-7.9 kg	8-8.9 kg	9-9.9 kg	10-10.9 kg	11-11.9 kg	12-13.9 kg	14-16.9 kg	17-19.9 kg	20-24.9 kg		25-29.9 kg	30-34.9 kg
AZT	60	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300	1	1
AZT (new annex E)	300; 10 mg/ml	6 ml	6 ml	6 ml	9 ml	9 ml	9 ml	9 ml	12 ml	12 ml	12 ml	0.5	0.5	0.75	300	1	1
AZT/3TC	60/30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/150	1	1
AZT/3TC/NVP	60/30/50	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/150/200	1	1
ABC	60	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300	1	1
ABC (new annex E)	300; 20 mg/ml	3 ml	3 ml	3 ml	4 ml	4 ml	4 ml	4 ml	6 ml	6 ml	6 ml	0.5	0.5	0.75	300	1	1
ABC/3TC	60/30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/150	1	1
ABC/3TC/NVP	60/30/50	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/150/200	1	1
ABC/AZT/3TC	60/60/30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	300/300/150	1	1
3TC	30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	150	1	1
3TC (new annex E)	150; 10 mg/ml	3 ml	3 ml	3 ml	4 ml	4 ml	4 ml	4 ml	6 ml	6 ml	6 ml	0.5	0.5	0.75	150	1	1
d4T	6	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	30	1	1
d4T (new annex E)	various; 1 mg/ml	6 ml	6 ml	6 ml	9 ml	9 ml	9 ml	9 ml	1x15 mg	1x15 mg	1x15 mg	1x20 mg	1x20 mg	1x20 mg	30	1	1
d4T/3TC	6/30	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	30/150	1	1
d4T/3TC/NVP	6/30/50	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	30/150/200	1	1
NVP	50	1	1	1	1.5	1.5	1.5	1.5	2	2	2	2.5	2.5	3	200	1	1
NVP (new annex E)	200; 10 mg/ml	5 ml	5 ml	5 ml	8 ml	8 ml	8 ml	8 ml	10 ml	10ml	10 ml	0.75	0.75	0.75	200	1	1
Lopinavir/ritonavir	100/25	n/r	n/r	n/r	n/r	n/r	n/r	n/r	1.5	1.5	1.5	2	2	2.5	100/25 * (paed)	3	3
Lop/rit (new annex E)	80/20 mg/ml	1 ml	1.5 ml	1.5 ml	1.5 ml	1.5 ml	1.5 ml	1.5 ml	2 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	80/20 mg/ml	3.5 ml	4 ml

* 3 tablets BD of 100/25 may be substituted with 2 tablets am and 1 tablet pm of 200/50
Note: higher doses of Lop/rit may be required when co-administered with enzyme-inducing drugs such as NVP, EFV; fosamprenavir, rifampicin.

Fig. 1. Paediatric antiretroviral dosing table, World Health Organization (2008).[17]

TABLE II. DOSING CONSIDERATIONS FOR INDIVIDUAL ANTIRETROVIRAL DRUGS INCLUDED IN THE REVISED WHO DOSING TABLE (2008) AND ADAPTED FOR THE ANTIRETROVIRAL DRUG DOSING CHART (2009)[18]

Drug	Target dosing range	Considerations
ABC	8 - 10 mg/kg/dose twice daily	Clearance in children <3 years old is increased, but recent data on once-daily dosing in children from 3 months of age suggest favourable Pk profile
AZT	180 - 240 mg/m^2 /dose twice daily	Twice-daily dosing is acceptable and preferred Dosing at the upper end of the range is recommended for central nervous system HIV disease; dosing at the lower end may be preferred in settings where anaemia is prevalent
d4T	1 mg/kg/dose twice daily	Needed as a priority product despite well-recognised longer-term toxicities (lipodystrophy), as it is initially well tolerated, is safer to use in anaemia than AZT, and has lower laboratory monitoring requirements Avoid over-dosing wherever possible (noting recent revision to adult dosing recommendation to reduce dose) and especially for extended periods to minimise toxicity
ddI	<3 months of age: 50 mg/m^2/dose; >3 months: 120 mg/m^2/dose twice daily	Enteric-coated formulations are preferred over the buffered form Needs to be given 1 hour before or 2 hours after food Once-daily dosing accepted over 6 years of age
3TC	4 mg/kg/dose twice daily	Clearance in children <3 years old is increased, and minimal observed toxicity allows for higher dosing in younger children (up to 5 mg/kg/dose twice daily)
NVP	A BSA dose range of 150 - 200 mg/m^2/dose twice daily is used to generate weight-band dosing	Under-dosing must be avoided wherever possible owing to low barrier development of HIV drug resistance A reduced dose (150 - 200 mg/m^2/dose once daily) is recommended for the first 2 weeks when initiating NVP treatment regimens Young children require a higher NVP dose relative to the NRTI components than delivered in current adult FDCs
EFV	By weight band (15 - 18.75 mg/kg/dose solid formulation or 19.5 mg/kg/dose suspension, once daily)	Dosing not established for children <3 years Suspension is over 30% less bio-available than solid formulations
LPV/rtv	Approved dose is 230/75.5 mg/m^2/dose twice daily; 300/75 mg/m^2/dose is recommended in children <2 years of age, if taken with NNRTI, or for PI-experienced patients	Clearance in children <2 years is increased Actual exposure depends on metabolism and inter-patient variability, which is considerable Heat-stable paediatric formulation recently approved (awaiting registration in SA)
RTV	Co-formulated with lopinavir (L:r ratio 4:1) For patients receiving rifampicin, additional RTV dosed at 0.75 x L/r dose to achieve L:r ratio of 1:1	Needed for use as a pharmacological booster with PI-based treatment and for children receiving rifampicin-based antituberculosis therapy

table and incorporating safety and efficacy end-points has been developed.

CONCLUSION

The use of weight-band ARV dosing approaches, adapted in accordance with locally available formulations and treatment programme conditions, is a key component of simplifying paediatric ART for health care providers as well as children and their caregivers, and will contribute to expanding treatment coverage for HIV-infected infants and children.

Acknowledgements

For assistance with the development, analysis and implementation of the Western Cape Antiretroviral Drug Dosing Chart (2007): Shenaaz Raiman (pharmacist), Heather Jaspan, Brian Eley, Mary-Ann Davies, Brenda Smuts, David Pienaar, Heli Moeng, staff at the HIV clinic at Red Cross War Memorial Children's Hospital, Cape Town and Nolungile HIV clinic, Khayelitsha.

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Target dose	Stavudine (d4T)	Lamivudine (3TC)	Zidovudine (AZT)	Didanosine (ddI)	Abacavir (ABC)	Efavirenz (EFV)	Nevirapine (NVP)	Lopinavir/ritonavir (LPV/rtv)	Ritonavir boosting (RTV)	Co-trimoxazole	Multi-vitamins	Target dose
	1mg/kg/dose TWICE daily	4-6mg/kg/dose TWICE daily	240mg/m^2/dose TWICE daily	90-120mg/m^2/dose TWICE daily	8mg/kg/dose TWICE daily	By wt. band ONCE daily	150mg/m^2/dose * TWICE daily	300/75mg/m^2/dose LPV/rtv TWICE daily	** ONLY as booster for LPV/rtv when on Rifampicin TWICE daily	ONCE daily	ONCE daily	
Available formul-ations	Sol. 1mg/ml Caps 15,20, 30mg	Sol. 10mg/ml Tabs 150mg (scored)	Sol. 10mg/ml Caps 100mg Tabs 300mg (not scored)	Tabs 25,50,100mg (dispersible in 30ml water) Caps 250mg EC	Sol. 20mg/ml Tabs 300mg (not scored)	Caps 50, 200mg Tabs 50, 200, 600mg (not scored)	Sol. 10mg/ml Tabs 200mg (scored)	Sol. 80/20mg/ml Tabs 200/50mg, 100/25mg	Sol. 80mg/ml	Sol. 40/200mg/5ml Tabs 80/400mg (scored)	Sol. Tabs (B Co)	**Available formul-ations**
Wt. (kg)												**Wt. (kg)**
<3	Consult with a clinician experienced in paediatric ARV prescribing for neonates (<28 days of age) and infants weighing <3kg									2.5ml	2.5ml	**<3**
3-3.9	6ml	3ml	6ml	avoid	3ml	Dosing <10kg not established	5ml	1ml	**1ml			**3-3.9**
4-4.9								1.5ml	**1.2ml			**4-4.9**
5-5.9	7.5mg: open 15mg capsule into 5ml water: give 2.5ml & discard rest			2x25mg tabs						5ml OR ½ tab		**5-5.9**
6-6.9		4ml	9ml				8ml					**6-6.9**
7-7.9	10mg: open 20mg capsule into 5ml water: give 2.5ml & discard rest				4ml							**7-7.9**
8-8.9												**8-8.9**
9-9.9												**9-9.9**
10-10.9	15mg: open 15mg capsule into 5ml water	6ml	12ml	1x50mg+1x25mg tabs am; 2x25mg tabs pm	6ml	200mg cap/tab	10ml	2ml twice daily OR 100/25mg tabs: 2 tabs am, 1 tab pm	**1.5ml		5ml	**10-10.9**
11-11.9				1x50mg+1x25mg tabs								**11-11.9**
12-13.9												**12-13.9**
14-16.9	20mg: open 20mg capsule into 5ml water	½ tab	2 caps am; 1 cap pm	2x50mg tabs am; 1x50mg+1x25mg tabs pm	7ml	200mg cap/tab + 50mg cap/tab	1 tab am; ½ tab pm	2.5ml twice daily OR 100/25mg tabs: 2 tabs twice daily	**2ml	10ml OR 1 tab		**14-16.9**
17-19.9				2x50mg tabs	8ml							**17-19.9**
20-24.9	20mg am; 30mg pm	1 tab am; 1/2 tab pm	2 caps	1x100mg tab+ 1x25mg tab twice daily OR 1x250mg EC cap once daily	10ml	200mg cap/tab + 2x50mg caps/tabs		3ml twice daily OR 100/25mg tabs: 3 tabs am, 2 tabs pm	**2.5ml			**20-24.9**
25-29.9	30mg	1 tab	1 tab		1 tab	200mg cap/tab + 3x50mg caps/tabs	1 tab	3.5ml twice daily OR 200/50mg tabs: 2 tabs am, 1 tab pm	**3ml			**25-29.9**
30-34.9						2x200mg caps/tabs		4ml twice daily OR 200/50mg tabs: 2 tabs am, 1 tab pm		2 tabs	1 tab	**30-34.9**
35-39.9								5ml twice daily OR 200/50mg tabs: 2 tabs twice daily	**4ml			**35-39.9**
>40						600mg tab						**>40**

* A lead-in dose of nevirapine is given for the first 14 days of treatment equivalent to half of maintenance dose i.e. usual maintenance dose but given once-daily. Increase to full maintenance dose after 14 days if no rash develops.

Compiled by J. Nuttall & S. Raiman for the Paediatric HIV/TB Policy Reference Group, Western Cape. Adapted from World Health Organisation guidelines, 2006 & 2008.

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Body Surface Area (BSA) $m^2 = \sqrt{\frac{\text{Mass (kg) x Height (cm)}}{3600}}$

Fig. 2. Antiretroviral drug dosing chart for children (2009) (copies available via National HIV Health Care Worker Hotline 0800 212 506).

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CLINICAL

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME IN CHILDREN

Helena Rabie[1], *FCP (Paed)*
Tammy Meyers[2], *FCP (Paed)*
Mark F Cotton[1], *PhD*

[1]*Department of Paediatrics and Child Health, Tygerberg Children's Hospital and Stellenbosch University, Tygerberg, W Cape*
[2]*Harriet Shezi Paediatric ARV Clinic, Chris Hani Baragwanath Hospital, Johannesburg*

Paradoxical deterioration due to immune reconstitution inflammatory syndrome (IRIS) occurs in up to 21% of children initiating antiretroviral therapy. Mycobacterial diseases are the most common, with BCG-vaccine adenitis predominating in infants and *Mycobacterium tuberculosis* (TB) in older children. The difficulty of diagnosing TB in HIV-infected children and the increasing risk of drug-resistant TB complicate the diagnosis and management of both paradoxical IRIS and post-antiretroviral therapy TB. History and clinical assessment remain key strategies in the management of these infants and children. There are no prospective studies investigating diagnostic criteria and therapeutic strategies in children.

Immune reconstitution inflammatory syndrome (IRIS) refers to an 'unexpected' and paradoxical clinical deterioration in the period immediately after initiation of antiretroviral therapy (ART). Diagnosis of IRIS relates to the time frame after initiation of antiretroviral therapy ART, response to ART and exclusion of alternative diagnoses. Boulware *et al.* proposed criteria for children.[1] There are fewer data on incidence, prevalence and clinical descriptions in infants and children than in adults. Studies report a prevalence of up to 21% in South African infants.[2] IRIS is commonly associated with mycobacterial infections, mainly bacille Calmette-Guérin (BCG), *Mycobacterium tuberculosis* and non-tuberculous mycobacteria (NTM).[2-5] Other conditions such as skin disease, herpes simplex, cryptococcal meningitis and immune diseases such as Guillain-Barré syndrome are also reported.[1,3] Age and geographical location are important determinants of the risk for each disease. Table I summarises the most pertinent paediatric literature.

M. TUBERCULOSIS IRIS

EPIDEMIOLOGICAL CONSIDERATIONS IN HIV-INFECTED CHILDREN

Tuberculosis (TB) is a common opportunistic infection in HIV-infected African children. Rates of 53.3 cases/100 patient-years are reported in children not on highly active antiretroviral therapy (HAART).[6] High rates of exposure to potentially infectious source cases are well documented in HIV-exposed infants[7] and rates of disease of 1 596 cases per 100 000 HIV-infected infants are documented in Cape Town.[8] Young age and HIV-related immunosuppression contribute to this high disease burden.

Recurrent episodes of TB are well documented and are caused by both relapse and re-infection.[9] In a cohort studied before and after widespread availability of ART, 30% of children with HIV and culture-confirmed TB had received prior TB therapy.[6]

Rates of drug-resistant TB vary between settings. Drug resistance was reported in 17% of HIV-infected children with TB, 6.8% having resistance to both rifampicin and isoniazid.[10] Children with prior TB therapy are at higher risk of resistance.[11] There may be an incomplete therapeutic response to 6 months of standard anti-TB therapy.[9]

Up to a third of children initiating HAART may be on anti-TB therapy.[6,12] Cohort data from low-resource settings indicate that the majority of children still initiate HAART at very low CD4 counts and with significant clinical disease.[13] These children are at high risk for IRIS and incident TB from new exposure to *M. tuberculosis.* With improved access to HAART, an up to 70% reduction in the incident TB can be achieved.[6,14]

DIAGNOSTIC CONSIDERATIONS

The diagnosis of TB in HIV-infected children remains difficult. Signs and symptoms overlap with advanced HIV. Clinical scoring tools have poor specificity in HIV-infected children.[15,16]

Sputum is difficult to collect in young children, and gastric washings are frequently not performed.[17] Culture yields from gastric washings and induced sputa are low in children. Although yields of up to 40%[18] have been reported in research settings, the yield in clinical settings is

lower.[19] In children with a high index of suspicion for TB, microbiological confirmation can be obtained in 55%, increasing to 80% with significant pulmonary infiltration.[16] Chest radiographs are difficult to interpret owing to ubiquitous chronic underlying HIV-associated lung disease. Tuberculin skin tests have a reduced sensitivity despite adjusting the extent of induration from 10 mm to 5 mm.[20] The value of interferon-gamma release assays in HIV-infected children is still under study. Negative results do not exclude TB,[21] and tests are expensive. Although failure of therapy for an opportunistic infection is considered an exclusion criterion for IRIS, IRIS has been diagnosed in adults with inadequately treated drug-resistant TB.[22] As the diagnosis of TB is seldom confirmed by culture and drug sensitivity is often not available, it may be difficult to differentiate IRIS from poor response to treatment and drug resistance. It may not be possible to confirm a response to HAART because of lack of access to virological testing. If events occur soon after initiation of therapy, significant reductions in viral load and clinical responses may not yet have occurred.

THERAPEUTIC CONSIDERATIONS

Current dosages of anti-TB medicines, especially isoniazid and rifampicin, are insufficient in all children; this is probably exacerbated in children with HIV, in whom malabsorption is common.[23-25]

Rifampicin reduces exposure to protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), thereby compromising HAART efficacy. Ritonavir-based HAART, previously recommended for co-treated children on PIs, has been associated with poorer virological outcomes.[26]

POST-HAART TB AND UNMASKING IRIS

Besides the general principles proposed by Boulware,[1] there are no proposed criteria to distinguish true IRIS from incident TB or missed disease prior to HAART initiation. Adult clinicians have suggested that all cases of TB after initiation of HAART should be termed post-HAART TB, with only cases occurring in the first 3 months accompanied by heightened clinical features classified as IRIS.[27] Data from cohort studies report TB rates of 3.4 - 6.2% in African children after initiating HAART[6,28] (Table I). In infants TB-IRIS is thought to be less common than BCG-IRIS.[2] Clustering of these cases in the first 100 days after HAART initiation is reported from cohort studies. In a large Ugandan study, a 2.7-fold increase in risk for TB was observed early after the initiation of HAART.[28] This could be due to inadequate screening procedures, as the converse was noted in a study where active screening was done.[6]

Few studies provide detailed assessment of the severity of disease, an essential component in distinguishing between IRIS, incident TB and disease missed prior to initiating HAART. Zampoli *et al.* described 7 children with post-HAART pulmonary TB IRIS, and 1 with additional extrapulmonary disease.[29] Three (43%) had received therapy prior to the initiation of HAART. Culture was positive in 4 of the 7 cases. Of these, 1 had multidrug resistance, having stopped anti-TB therapy 3 weeks before initiating HAART. All chest radiographs showed significant adenopathy with airways compression, extensive parenchymal infiltration and pleural reactions.[29] Although all IRIS is associated with significant inflammatory response, radiological findings are similar in HIV-infected children not on HAART.[10] Clinicians therefore need to judge the relative severity of these conditions. Exposure to *M. tuberculosis* shortly after initiation of HAART could conceivably present as post-HAART TB IRIS.[30] This is especially relevant in children immunologically primed by receiving BCG at birth.

IRIS caused by both BCG and TB in the same patient is now well documented in two prospective paediatric cohorts. In the NEVEREST study 50% of children with TB also had BCG IRIS.[2] In the CHER cohort, 19% of children with BCG IRIS adenitis also had TB IRIS.[31]

PARADOXICAL IRIS

Delaying the initiation of ART in TB cases with severe immunodeficiency is associated with increased HIV-related mortality.[32] Currently the World Health Organization (WHO) recommends that children with severe immune suppression or stage 4 disease should initiate ART 2 - 8 weeks after the initiation of anti-TB therapy.[33]

The basic diagnostic criteria for IRIS[1] should be met first when diagnosing paradoxical IRIS. The proposed case definitions for TB paradoxical IRIS, although appropriate for well-resourced settings, are problematic in lower-resource settings. This is due to the diagnostic uncertainty of TB in HIV-infected children and difficulty in excluding alternative diagnoses and confirming a response to ART because of inability to measure CD4 counts or viral load, especially in rural areas.

Few data exist on the risk of paradoxical IRIS. The study from Uganda reports only 2 cases of paradoxical IRIS.[27] Zampoli *et al.* recently described the clinical events in 4 children receiving anti-TB therapy for 21 - 59 days before initiation of ART, who subsequently developed TB IRIS between 6 and 105 days later. Skin test conversion was documented in 1 child and was positive at the time of exacerbation in another. Two children presented with deterioration of pulmonary TB, 1 developed local adenitis and another abdominal adenitis. One child died.[29]

There is little information on clinical features and management of neurological paradoxical IRIS in children. In adults these account for 12% of cases of paradoxical TB IRIS.[34] Similarly, intra-abdominal TB IRIS is com-

TABLE I. COMPARISON OF STUDIES ILLUSTRATING ASPECTS OF PAEDIATRIC IRIS

	Smith *et al.*[2] All IRIS	Puthanacit *et al.*[3] All IRIS	Nuttall *et al.*[46] BCG only	Zampoli *et al.*[29] TB only	Walters *et al.*[6] All TB and aspects of BCG
Age (all)	8 months	7.9 years		8 - 121 months	23.5 months
Episodes/children (%)	34 episodes /169 children (21%)	32 episodes/153 children (19%)	21 episodes /331 children (6.3%)	11 cases	10 unmasking TB, 4 paradoxical
Age, cases v. controls (*p*-value)	7 months v. 10 months (0.007)	8.2 years v. 7.8 years (0.50)	5 months v. 27 months (<0.001)		
CD4%, cases v. controls (*p*-value)		3.1 v. 5.5 (0.02)	12.3% v. 12.0% (0.55)	10.3% (cases only)	
Absolute CD4 count, cases v. controls (*p*-value)	741 v. 1 075 (0.0148)				
Log baseline HIV RNA copies/ml, cases v. controls (*p*-value)		5.37 v. 5.37 HIV RNA copies/ml (0.96)	6.1 v. 5.6 (0.001)		
Viral load >750 000 (%)	79% v. 55% (0.044)				
Time to event (mean (range))	16 days (7 - 115)	6 weeks (2 - 21)	34 days (15 - 60)		
BCG	24/34	2/32	21/21		
TB	6/34	3/32		11/11, 4 paradoxical IRIS	14/14
TB and BCG	6/34				
MAC		4/32			
NTM		5/32			
Herpes zoster		7/32			
Herpes labialis	1/34	6/32			
Herpes encephalitis		1/32			
Cryptococcal meningitis		3/32			
Cytomegalovirus	1/34				
PCP	1/34				
Seborrhoeic dermatitis	1				
Bacterial sepsis	2				
GBS		1/32			

BCG = Bacille Calmette-Guérin; TB = tuberculosis; MAC = *M. avium-intracellulare;* NTM = non-tuberculous mycobacteria; PCP = *Pneumocystis* pneumonia; GBS = group B streptococcal disease.

mon in adults, occurring in 37% of cases.[35] Although paediatric cases do occur (Helena Rabie – unpublished data), little is known about the prevalence in children.

It is challenging to exclude drug-resistant TB and failure of TB therapy for other reasons in these children. Resistance was common in an adult series from Cape Town.[22] The case in Fig. 1 illustrates the diagnostic difficulties in a setting of paradoxical IRIS and resistance to TB therapy.

GENERAL EVALUATION

Contact with a source case has been documented in 30 - 54% of HIV-infected children with TB.[6,10] TB can therefore be prevented and detected through a careful history looking for a source case in the household and extended social circle. In older children and adolescents transmission may occur outside the family due to social mobility, and it is likely that a history of contact will be a less sensitive marker to distinguish incident TB from IRIS.

Reviewing adherence to anti-TB therapy and ART is essential to evaluate children with suspected paradoxical TB IRIS. Documentation of suspected contact with a source patient who may have drug-resistant TB is also crucial. In

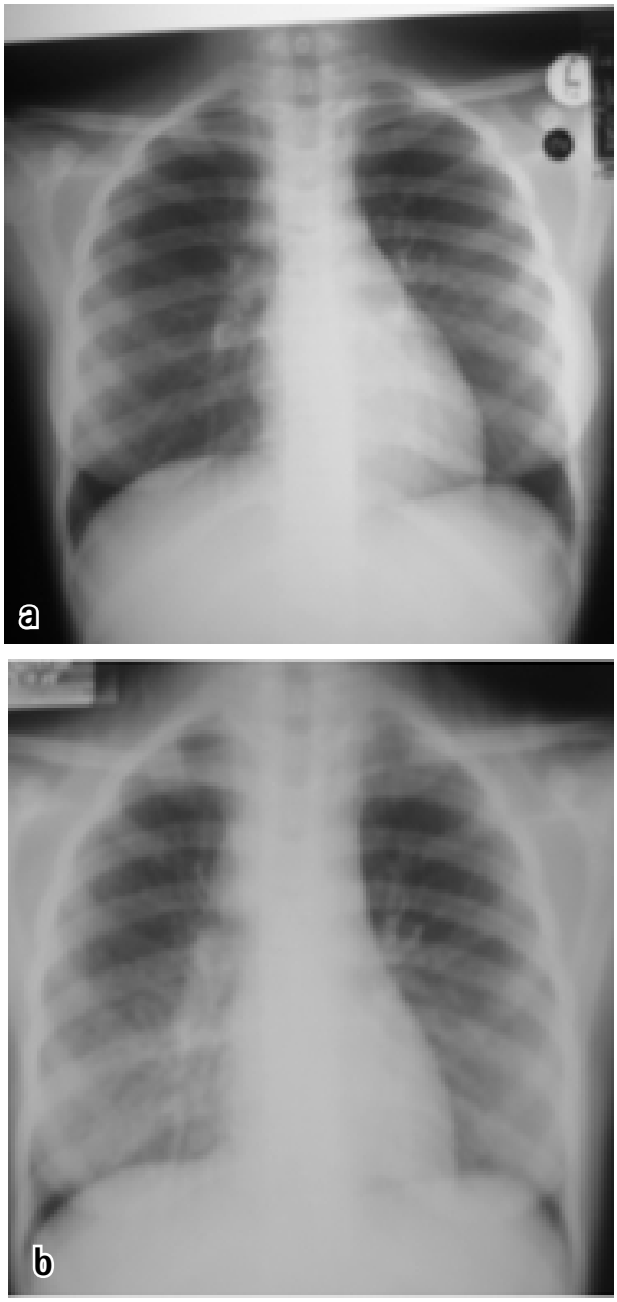

Fig. 1. Drug-resistant TB presenting as paradoxical IRIS in a 12-year-old girl with pulmonary and abdominal TB and severe immune suppression (chest radiograph a). She was sputum smear positive and had a CD4 count of 31 cells/µl. Anti-TB therapy with four drugs was initiated and she responded well, smear conversion taking place within 3 weeks. ART was started 3 weeks after initiation of TB therapy, and 7 days later she developed a high fever, severe abdominal pain and food intolerance. The sputum smear was now positive, and a chest radiograph (b) suggested miliary TB. Steroids were added with some clinical improvement. Rifampicin resistance was confirmed after 48 days on TB therapy and 27 days on ART.

adults diagnosed with paradoxical TB IRIS, resistance is a major clinical confounder.[22] Weight gain on therapy may be an important and measurable clinical marker supporting IRIS rather than clinical deterioration. This information, together with clustering in the first 100 days, may allow for a possible differentiation between incident TB and IRIS in younger children. Culture for *M. tuberculosis* and drug sensitivity testing should be conducted whenever possible. Clinical judgement should guide clinicians as to additional investigations needed to exclude additional diagnoses such as acute bacterial infections, drug reactions and other opportunistic infections or malignancies.

MANAGEMENT

Children are at higher risk than adults of death and hospitalisation in the period immediately after HAART initiation. Mortality of 17.4/100 000 patient-years in the first 3 months of therapy has been reported. Up to 30% require hospitalisation in the first 6 months on therapy. Two-thirds of the admissions are related to bacterial infection and pneumonia.[36,37] Withholding antibiotic therapy and other interventions at initial presentation is therefore very dangerous when TB IRIS is suspected.

As in adults, therapy for TB IRIS includes the anti-TB therapy and continuation of HAART. However, if the IRIS event is life-threatening or likely to cause permanent disability (i.e. TB meningitis with clinical deterioration), HAART may be discontinued temporarily. Children on PIs can stop all drugs simultaneously. There is a significant risk for resistance when stopping efavirenz or nevirapine.[38] Clinicians need to weigh the risk of inducing NNRTI resistance against that of continuing either NRTIs or boosted lopinavir/ritonavir for 7 - 14 days. The safety of these strategies is unknown in this scenario.

Steroids improve outcomes for adults with moderate to severe TB IRIS, but there are no randomised studies in children.[39] As in adults, clinicians must weigh the risk of resistant TB prior to starting steroid therapy. Other modalities used (but not studied) include non-steroidal anti-inflammatory drugs (NSAIDs), thalidomide and leucotriene receptor antagonists.[40-44] Despite the lack of data, it is reasonable to stratify the use of supportive therapy as follows: NSAIDs for mild to moderate disease, and steroids for severe disease. In cases where there is a prior indication, i.e. meningitis, steroids should always be used. It is unclear whether pre-emptive steroids or NSAIDs can prevent IRIS (a trial in adults is underway).

BCG-RELATED IRIS

BCG is the most common mycobacterial IRIS in infants given BCG at birth.[2] Vaccine site ulceration and abscess formation, ipsilateral adenitis and exacerbation of disseminated disease occur.[45] Where ART is delayed until clinically indicated, 6% of all children and 14% of infants experience BCG-related adverse events. In this setting, age at initiation is the most important risk factor.[2,46] When children access therapy early and at a younger age, a low CD4 count is the most important predictor.[45] Although there is a significant reduction in the risk of IRIS with early initiation of ART adverse events are common in these infants also.[31]

The diagnosis of IRIS remains clinical. Where systemic disease is suspected, extensive investigation may be required. Although no prospective studies have been conducted, it is likely that local and regional IRIS requires no specific therapy. However, disseminated disease requires aggressive therapy that should be discussed with an expert. Danish strain BCG is resistant to current standard doses of isoniazid as well as to pyrazinamide and ethionamide.[47] Induction of resistance in inappropriately treated cases with systemic disease has been documented.[48]

NON-TUBERCULOSIS MYCOBACTERIA

One study from Thailand reports on non-tuberculosis mycobacterial IRIS in children. Of 153 children initiating therapy at a median age of 7.9 years, 9 had IRIS caused by non-tuberculosis mycobacteria, 2 with paradoxical deterioration and 7 with unmasking disease. The rate was 5.9 cases per 100.[5] There are no data for South African children, although cases do occur (Helena Rabie - unpublished data).

IRIS INVOLVING SKIN CHANGES

Skin changes are the most common form of IRIS in adults, but there are fewer data in children. Unpublished data from KwaZulu-Natal reported by Boulware in a review on IRIS indicated that 53% of children had a new onset of rash after the initiation of HAART.[1] These included molluscum contagiosum (8%), tinea capitis (20%), warts (16%), impetigo (12%), herpes zoster (5%), and other fungal rashes (24%).[1] Earlier cohorts reported that 11% of children developed herpes zoster. Children at risk were negative for varicella antibody despite a previous history of varicella and had severe immunodeficiency before treatment.[49]

Exacerbation of warts and molluscum contagiosum is commonly seen. If areas such as the face are involved, this disfigurement can be very disruptive and may lead to non-adherence.

OTHER PHENOMENA

Cryptococcus neoformans is common in South African adults[50] but less common in children. In children <15 years of age, the incidence is 1 per 100 000 population.[51] *C. neoformans* IRIS of both the central nervous system and the lungs occurs occasionally.[52]

Guillain Barré syndrome, myocardial dilatation, exacerbation of JC virus progressive multifocal leucoencephalopathy, leprosy, Kaposi's sarcoma, cytomegalovirus, *Pneumocystis* pneumonia (PCP), opsoclonus-myoclonus syndrome, toxoplasmosis and other entities have been reported in adults and in children.[3,41,53-55]

CONCLUSION

IRIS is common in children. BCG is important in infants and TB is more prevalent in older children. Although the morbidity is thought to be low, IRIS may be diagnostically challenging and carry a high morbidity. A higher drug burden may result in decreased therapeutic success, with possible non-adherence and more potential for drug interactions as well. A careful history and clinical review remain important tools in the diagnosis and management of these conditions.

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CLINICAL

LIPODYSTROPHY SYNDROME IN HIV-INFECTED CHILDREN ON HAART

Steve Innes[1], *MB BCh, MRCPCH*
Leon Levin[2], *MB BCh, FCPaed (SA), DTM&H*
Mark Cotton[1,3], *MB ChB, MMed, PhD, FCPaed, DTM&H, DCH (SA)*
[1]*KID-CRU (Children's Infectious Diseases Clinical Research Unit), Tygerberg Children's Hospital and Stellenbosch University, Tygerberg, W Cape*
[2]*Paediatric HIV Programmes, Right To Care, Johannesburg*
[3]*Paediatric Infectious Diseases Unit, Department of Paediatrics and Child Health, Tygerberg Children's Hospital*

Lipodystrophy syndrome (LD) is common in HIV-infected children, particularly those taking didanosine, stavudine or zidovudine. Lipo-atrophy in particular causes major stigmatisation and interferes with adherence. In addition, LD may have significant long-term health consequences, particularly cardiovascular. Since the stigmatising fat distribution changes of LD are largely permanent, the focus of management remains on early detection and arresting progression. Practical guidelines for surveillance and avoidance of LD in routine clinical practice are presented. The diagnosis of LD is described and therapeutic options are reviewed. The most important therapeutic intervention is to switch the most likely offending antiretroviral to a non-LD-inducing agent as soon as LD is recognised. Typically, when lipo-atrophy or lipohypertrophy is diagnosed the thymidine nucleoside reverse transcriptase inhibitor (NRTI) is switched to a non-thymidine agent such as abacavir (or tenofovir in adults). Where dyslipidaemia is predominant, a dietician review is helpful, and the clinician may consider switching to a protease inhibitor-sparing regimen or to atazanavir.

Antiretroviral agents have led to dramatic advancements in life expectancy and quality of life for people living with HIV/AIDS. Despite this progress, lower-income countries are forced to use older, less expensive antiretrovirals such as stavudine, which are associated with a relatively high frequency of late toxic effects. Nevertheless, the older antiretrovirals are likely to remain the backbone of the national first-line highly active antiretroviral therapy (HAART) regimen in South Africa for the foreseeable future due to cost constraints.[1,2] One of the more common late toxic effects of older antiretrovirals is lipodystrophy syndrome (LD).

LD is an umbrella term referring to peripheral lipoatrophy (LA), central lipohypertrophy (LH), and dyslipidaemia associated with insulin resistance.[3,4] These may occur alone or in combination. Although LD was initially thought to be a syndrome of fat redistribution resulting in peripheral LA combined with central LH, preliminary data from the FRAM study in adults (Study of Fat Redistribution and Metabolic Change in HIV infection)[5] indicate that LH and LA are less closely linked than was previously presumed. Other authors have also noted that LH and LA often occur independently of one another.[6] In addition, dyslipidaemia associated with HAART may occur in the absence of LA or LH.[7]

LA results in disfigurement, particularly of the face (Figs 1 - 6), which can lead to stigmatisation and even forced disclosure of HIV status. This disfigurement has a major impact on adherence, particularly in adolescents.[3,6,7] In addition, the long-term health consequences of LD in HIV-infected children, who require lifetime antiretrovirals, are considerable: the most important consequence arises from dyslipidaemia and insulin resistance, which are known to significantly accelerate lifetime risk for cardiovascular disease in HIV-infected adults with LD.[8] It is unclear whether transient drug-induced dyslipidaemia in childhood increases the lifetime risk of cardiovascular disease in children.[9,10] Nonetheless, these negative health outcomes are of concern given that the prevalence of HAART-related LD in resource-limited settings may be as high as 47% after 2 years of therapy.[6]

The mechanisms of LD have not yet been firmly established. The mechanism of LA is related to mitochondrial damage, particularly in adipocytes.[11] HAART-related apoptosis of adipocytes and suppression of pre-adipocyte differentiation have been described in protease inhibitor (PI)-induced LA.[12] A similar mechanism may occur in nucleoside reverse transcriptase inhibitor (NRTI)-induced LD, since it is known that NRTIs such as stavudine can damage adipocyte mitochondria[11] and cause a reduction in functioning mitochondria in adults.[13] Other chronic toxic effects such as lactic acidosis and peripheral neuropathy have also been associated with mitochondrial dysfunction.[14,15] It has been suggested

that unknown agents released from damaged mitochondria in adipocytes may directly trigger apoptosis which leads to subcutaneous fat loss. Quantification of mitochondrial DNA in peripheral leucocytes may be an early warning sign of impending LD in patients exposed to antiretrovirals.[16,17] Circulating growth hormone (GH) levels are significantly reduced in patients with LA/LH, and this is likely to aggravate the abnormal fat distribution.[18]

HAART-related dyslipidaemia is thought to be mediated by a different, though related, mechanism: PI-induced alterations in adipokines and pro-inflammatory cytokines cause an increased production of triglycerides and cholesterol in hepatocytes, while simultaneously inhibiting glucose uptake in peripheral adipocytes.[19]

RISK FACTORS

The risk of developing LD is strongly related to the dosage and duration of exposure to antiretroviral agents. The thymidine NRTIs (zidovudine and stavudine) and didanosine have been linked to LA/LH.[20,21] In comparison, abacavir, tenofovir, and lamivudine have minimal or no LA/LH-causing effect.[22] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are considered a less potent cause of LA.[7] Although efavirenz has been associated with lipomastia in some children, this usually resolves spontaneously without withdrawal of efavirenz.[23,24] PIs have been linked to dyslipidaemia,[25] and less strongly to LA/LH.[21,26]

Stavudine, in particular, has been found to be a potent cause of LA in children when taken in the standard paediatric dose of 1 mg/kg/dose twice daily.[3,7,27,28] Owing to the long-term toxicity of this dose, stavudine is now rarely used in the developed world. A review by Hill *et al.*[29] has recently led the World Health Organization (WHO) to recommend a reduction in the standardised dose of stavudine for adults weighing over 60 kg from 40 mg to 30 mg twice daily,[30] since it has been shown that a reduced dose results in a markedly lower risk of LD, while maintaining excellent antiviral efficacy.[31,32]

The recommended dose of stavudine for children, however, has not yet been reduced. Since the dose of stavudine is a major risk factor for the development of LD,[33] it would be reasonable to expect that the incidence of LD will fall when a lower dose is employed. The current standard paediatric dose of stavudine (1 mg/kg/dose twice daily) was extrapolated from the pharmacokinetic parameters of the adult dose of 40 mg twice daily, using data from a few small but well-controlled paediatric pharmacokinetic studies[34-36] which showed that an oral dose of 1 mg/kg/dose twice daily in children under 12 years results in plasma exposure similar to that of adults taking 40 mg twice daily, and that an oral dose of 0.5 mg/kg/dose twice daily in children results in plasma exposure similar to that of adults taking 20 mg twice daily.

Significance of lipodystrophy syndrome

- Lipodystrophy syndrome (LD) is common in HIV-infected children, particularly in those taking didanosine, stavudine or zidovudine.
- Lipo-atrophy (LA) (a component of LD) causes major stigmatisation and interferes with adherence.
- LD may have significant long-term health consequences, particularly cardiovascular.
- LA is largely permanent, so the focus remains on early detection and arresting progression.

What to look out for

- Look for a lean, muscular appearance of face and limbs with prominent limb veins due to loss of subcutaneous fat tissue.
- Compare the child's tricep and bicep skin-fold thickness with your own as a rough guide.
- Shrinking buttocks with or without an enlarging abdomen may be monitored using a waist-to-hip ratio (WHR).
- Children on HAART should have their blood lipids measured routinely every year.

What to do

Where subcutaneous LA or lipohypertrophy is diagnosed:

- The most likely offending NRTI should be switched to abacavir (or tenofovir in adults).

Where dyslipidaemia is predominant:

- A dietician review is helpful.
- Consider switching to a PI-sparing regimen or to atazanavir.
- Look for insulin resistance.
- Statins and metformin are only used in extreme cases.

Particular mitochondrial DNA sub-groups (haplogroups) have been associated with a vulnerability to developing LA after exposure to HAART.[37] A recent study showed that Caucasian American men on HAART who have the H mitochondrial haplogroup were at significantly increased risk of LA.[37] In addition, certain mitochondrial DNA mutations may make an individual more vulnerable to developing LD when exposed to antiretroviral agents. This may occur because variations of mitochondrial DNA in adipocytes may reduce the efficiency of energy production or lead to increased oxygen free-radical production, resulting in a reduced mitochondrial reserve and an increased vulnerability to apoptosis when exposed to mitochondrial toxins such as antiretrovirals.

DIAGNOSIS

A complex set of diagnostic criteria for the diagnosis of LD has been developed for adults by Carr *et al.*[38] Equivalent diagnostic criteria for children have not been formally defined. Most clinicians employ a combination of objective anthropometric and biochemical measurements and a subjective assessment in order to diagnose LD in children.[6,7,33,39,40] Physical signs in children are due to loss of subcutaneous fat in limbs, buttocks and face, with or without accumulation of intra-abdominal visceral fat. Loss of limb fat results in prominent limb veins and a well-defined, muscular appearance of limbs in the presence of a normal or enlarged abdomen. Reduced skin-fold thickness (SFT) may be subjectively assessed by comparing it with one's own SFT as a rough guide.

Loss of buttock fat, with or without enlargement of the abdomen, results in a greatly increased waist-to-hip ratio (WHR). Breast enlargement and buffalo hump may occur after puberty. Other useful anthropometric measurements include mid-upper arm circumference (MUAC) and waist circumference, from which the waist-to-MUAC ratio can be calculated. SFT measurements may be used to calculate the torso-to-arm ratio (TAR) as follows: TAR = [subscapular + suprailiac SKF]/[bicep + tricep SFT]. A TAR z-score of >2.0 has been used as a diagnostic criterion in some studies.[39]

As HAART-related dyslipidaemia may occur independently of LA/LH,[5-7] children on HAART should have their blood lipids measured routinely at least once a year.

Facial fat loss is often subtle and difficult to detect unless severe. The facial muscles are not normally noticeable because they are covered in fat. Loss of facial fat results in a lean, muscular appearance of the face with deep laugh-lines when smiling. An old photograph may be helpful. Figs 1 and 2 show a child with mild LA of the face. Some recovery is seen 4 years after changing from a stavudine-containing regimen (Fig. 3). Fig. 4 shows a child with moderate facial LA. Figs 5 and 6 show a child with severe facial LA. Her LA was already advanced when she was changed from a stavudine-containing regimen 4 years previously, and is unlikely to improve.

To date there are limited data comparing the sensitivity and specificity of anthropometric and biochemical diagnostic criteria against a gold standard such as dual-energy X-ray absorptiometry or magnetic resonance imaging to diagnose early LA/LH in HIV-infected children. Studies are underway to define a practical set of diagnostic criteria to detect early LD in children in resource-limited settings. Since at least 30% of peripheral fat must be lost before LA becomes visibly evident,[41] it is hoped that some combination of anthropometric and biochemical measures will have reasonable sensitivity and specificity to detect LA/LH in children before it causes noticeable disfigurement (S Innes *et al.* – unpublished data). This will be an important contribution to paediatric HIV care in the developing world.

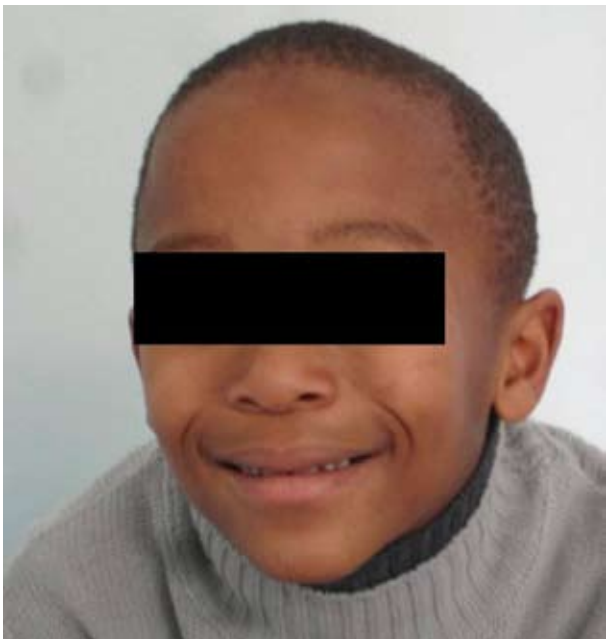

Fig. 1. Mild LA of the face, front view.

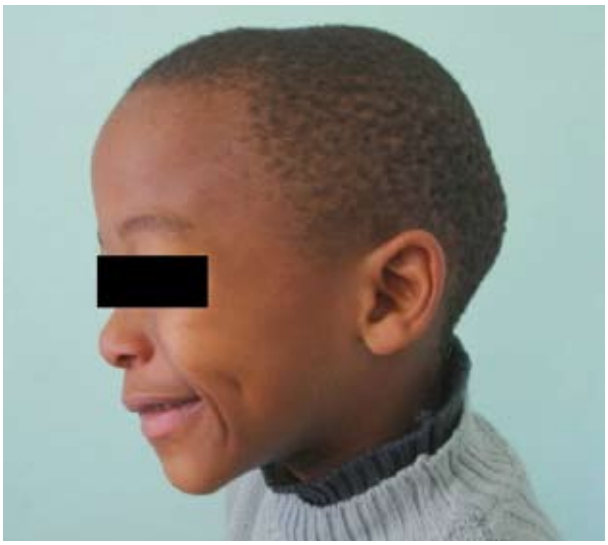

Fig. 2. Mild LA of the face, side view.

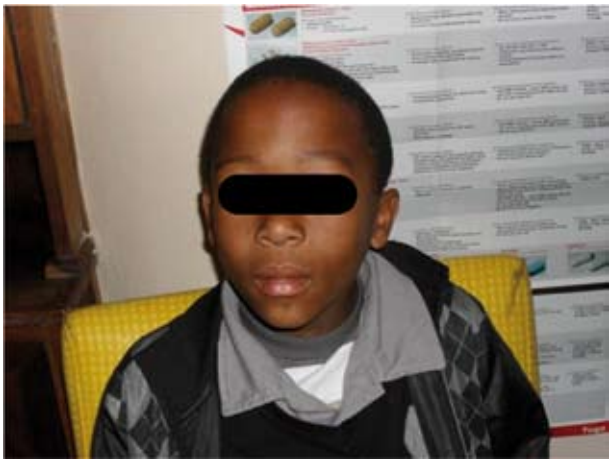

Fig. 3. The same child as in Fig. 1. Some recovery is seen 4 years after withdrawal of stavudine.

MANAGEMENT

Since the disfiguration caused by LD is largely permanent, the focus of management is on early detection and arrest of progression. Once identified, the most likely offending drug is usually withdrawn in an attempt to prevent progression, and is replaced by a less LD-inducing antiretroviral. Where dyslipidaemia is identified, diet and lifestyle modification are essential. If severe and persistent (total cholesterol >13 mmol/l or triglycerides >8.5 mmol/l),[1] the PI may be switched to a PI-sparing agent or changed to atazanavir/ritonavir (ATV/r), which has less effect on blood lipids.[21] The effect of statins in lowering triglycerides and cholesterol is well established;[42] however, statins are only licensed for use in children over 12 years of age. The potential interaction of statins with PIs must be borne in mind. Metformin has been shown to be effective for LD-related insulin resistance in adults[43] and for obesity-related insulin resistance in HIV-uninfected children.[44] However, metformin is rarely used in LD-related insulin resistance in children.

When LA/LH is diagnosed, significant benefit in halting progression has been shown from switching the thymidine NRTI to a non-thymidine agent such as abacavir.[21] Tenofovir is generally avoided in children because of renal toxicity and osteopenia. However, there may be a place for switching to tenofovir in older children.[45] This switch typically arrests progression of LA/LH, and may result in a small degree of reversal if LA is caught early. Various authors have demonstrated that the more advanced the LA, the less likely it is to reverse when the offending drug is removed.[46,47] Intradermal injections of a biodegradable filler such as poly-L-lactic acid (Sculptura) can ameliorate the aesthetic effect of facial LA in adults,[48] but this treatment is not appropriate for children. In addition, the cost is significant and the effect is not permanent and injections may need to be repeated. Uridine (NucleomaxX) partially reverses the mitochondrial toxicity caused by thymidine NRTIs, and may have a small but beneficial effect on disfiguring LA. Uridine is not currently available in South Africa, and it has no effect on dyslipidaemia.[49] Growth hormone-releasing hormone analogues (GH-RH) are helpful in the treatment of LA/LH.[50] The mechanism probably involves reversing the reduced GH levels that are consistently found in patients with LA/LH. Although the side-effect profile of GH-RH therapy is attractive, the cost is prohibitive. Future treatments may involve adipokines such as leptin, but these remain experimental.[21]

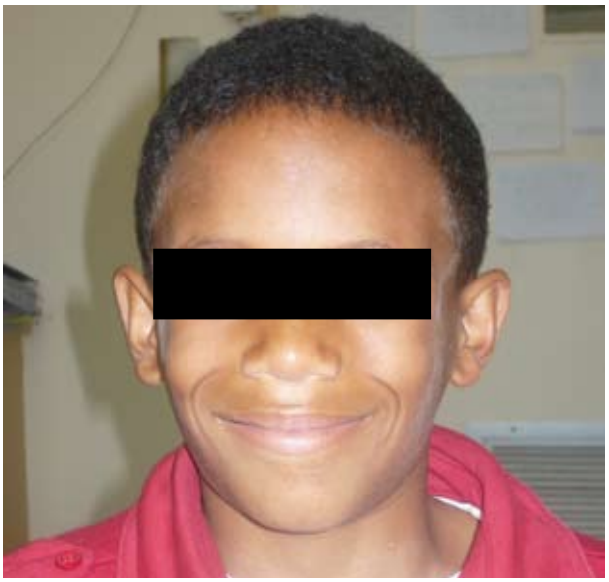

Fig. 4. Moderate LA of the face, front view. Note the loss of the buccal fat pad, resulting in lean, muscular appearance of the face with deep laugh-lines.

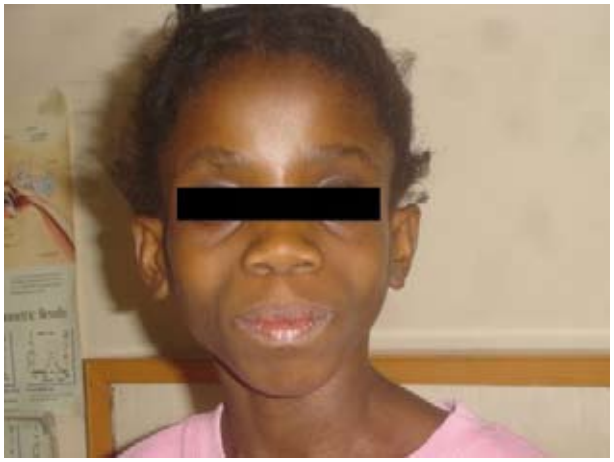

Fig. 5. Severe LA of the face, front view. This patient's LA was already advanced when she was changed from a stavudine-containing regimen 4 years previously. Her LA is unlikely to improve.

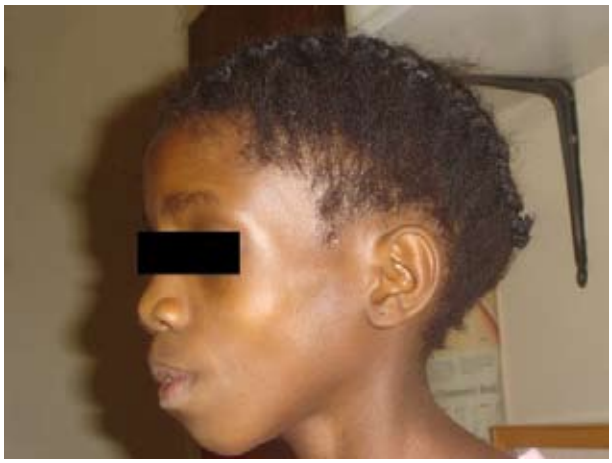

Fig. 6. Severe LA of the face, side view.

CONCLUSION

Research into reducing the paediatric dose of stavudine is urgently needed in order to minimise the risk of LD without compromising antiviral efficacy, since the number of at-risk HIV-infected children exposed to long-term stavudine therapy in South Africa is very large. In addition, non-thymidine NRTIs such as abacavir and tenofovir should be more widely available, particularly in the public sector.

Further research is needed to isolate the particular mitochondrial mutations that make a child vulnerable to LD. This may help public sector clinicians to predict which children should avoid thymidine NRTIs and rather be started on a more expensive, less LD-inducing antiretroviral regimen.

Finally, since effective treatment of LD is difficult and remains beyond the reach of resource-limited rural communities, early detection is paramount. It is essential to define a simple set of diagnostic criteria to identify early LD in children that can be easily implemented in resource-limited settings. This will allow the progression of LD to be halted before it causes noticeable disfigurement and stigmatisation. Children should be switched from stavudine (or zidovudine) to abacavir (and adults to tenofovir or abacavir) at the slightest sign of LD.

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ABACAVIR: ITS USE AND HYPERSENSITIVITY

Helena Rabie[1], *FCP (Paed)*
Kristin Lorenc Henning[1], *MB ChB, DCH*
Pierre Schoeman[2], *MB ChB, MMed (Clin Path)*
Nico de Villiers[2], *PhD (Hum Gen)*
G H J (Oubaas) Pretorius[2], *PhD (Biochem)*
Mark F Cotton[1], *PhD*
[1]*Department of Paediatrics and Child Health, Tygerberg Children's Hospital and Stellenbosch University, Tygerberg, W Cape*
[2]*PathCare Laboratories, N1 City, Goodwood, W Cape*

Abacavir, a nucleoside reverse transcriptase inhibitor, is useful in first- and second-line HIV therapy and as a substitute for stavudine and zidovudine when toxicity is a problem. Although it is safe and well tolerated, a life-threatening hypersensitivity reaction can occur. The risk for developing this reaction relates to the presence of specific genotypes, especially HLA-B*5701.

Abacavir (ABC), a nucleoside reverse transcriptase inhibitor (NRTI), combined with lamivudine (3TC), has a better short- and long-term outcome than 3TC combined with zidovudine (ZDV) as first-line HIV therapy.[1,2] In addition, children failing ABC/3TC-based first-line therapy do not select thymidine NRTI-related mutations, allowing for better choice in second-line therapy.[2] With current first-line options, both first-line (stavudine (d4T)) and second-line therapy (ZDV) include a thymidine-based NRTI, thus compromising second-line regimens.[3-5] In well-selected children, ABC is also an important drug in second-line and salvage therapy.[6]

Of all the NRTIs, ABC is associated with the lowest rate of mitochondrial dysfunction. Types of dysfunction include lactic acidosis, peripheral neuropathy and lipo-atrophy. Substitution of d4T for ABC improves mitochondrial indices and reduces adipocyte apoptosis.[7] In adults, switching from d4T to ABC was superior to switching from d4T to ZDV.[8] In older children, once-daily use of ABC has also been shown to be effective, thereby facilitating adherence and improving patient satisfaction, particularly when all drugs are given once daily.[9,10]

Despite these advantages, ABC is rarely used as part of first-line therapy in South Africa owing to cost. Tenofovir, commonly used in adults experiencing NRTI adverse events, is not licensed for children. With large cohorts of children now on antiretroviral therapy for long periods of time, increased use of ABC is likely as NRTI adverse events become apparent. Currently, the National Department of Health permits using ABC when there have been adverse events related to other NRTIs.

Of concern is the severe and life-threatening hypersensitivity reaction (HSR) that occasionally occurs, necessitating permanent discontinuation of ABC.

EPIDEMIOLOGY AND ESTIMATION OF RISK FOR HSR

ABC HSR has been reported in adults and children. The prevalence in clinical trials varies.[11] In a European trial of first-line therapy, where 92 children were initiated on ABC, 4 (4.3%) terminated ABC for adverse reactions, 1 case (1%) being considered an HSR. There is clear heterogeneity in risk according to ethnic groups, with Caucasians at higher risk and a 40% reduction in risk for African Americans. In the ARROW study of >1 200 HIV-infected children in Uganda and Zimbabwe, HSR was reported in 0.2% of the children.[12]

Other factors that may be protective are male sex and more advanced disease. However, this assessment was performed before identification of the genetic link to HSR.[13]

HLA-B*5701 AND HSR

An association with ABC HSR was described with HLA-B*5701, HLA-DR7 and HLA-DQ3. If all three markers are present, the positive predictive value for HSR is 100% with a negative predictive value of 97%. HLA-B*5701 alone is highly predictive.[14]

It is clear that the varied distribution of the HLA-B*5701 genotype is responsible for variability of the risk of ABC HSR between races and studies.[15] Studies from the USA indicated that this mutation is more prevalent among white and Hispanic persons than African Americans.[16] In Korea the HLA-B*5701 genotype and ABC HSR are rare.[17]

In the PREDICT-1 study, where patients with HLA-B*5701 did not receive ABC, 3.4% of patients given ABC were diagnosed with HSR but no cases could be confirmed with patch testing (a research tool only).[18] Prospective screening for HLA-B*5701 in patients and

avoidance of ABC in positive patients is effective in reducing HSR, and this is now the standard of care in the First World. Over-diagnosis of HSR is well documented in the absence of testing.[19] A reduction in confirmed cases occurs when routine testing is performed.[18]

Despite the availability of testing and the recommendation to test, there is a debate as to the cost effectiveness and cost benefit of testing in ethnic groups where HLA-B*5701 is not prevalent.[17]

There are no data on the prevalence of HLA-B*5701 in the various South African ethnic groups. Full genetic screening for HLA-B*5701 is very costly. Cheaper methods involving PCR for small sequences of the gene are currently under review. Although full testing is available in South Africa, patients in the public sector do not have access. We recommend that testing be offered to all patients where affordable, regardless of ethnic group, until more information is available. However, it is reasonable to use ABC without prior screening if there is no alternative.

It is important to remember that HSR has been reported in patients negative for HLA-B*5701.[20] In patients in whom HSR reaction was diagnosed and who subsequently tested negative for HLA-B*5701, ABC remains contraindicated.

CLINICAL FEATURES AND DIAGNOSIS OF ABC HSR

Diagnosis of ABC HSR is complicated by its subtle initial features. Also, other drugs such as trimethoprim-sulfamethoxazole, nevirapine and efavirenz are known to cause hypersensitivity and should be recognised. Distinguishing the ABC HSR from other drug-related adverse events, intercurrent infections and even immune reconstitution inflammatory syndrome may be particularly difficult when ABC is used as first-line therapy, as all drugs are initiated simultaneously. In addition, ABC initiation may lead to symptoms that are similar but not related to HSR, including nausea and vomiting, fever and rash. These reactions are usually mild.

Ninety-four per cent of patients who experience HSR do so within 6 weeks after initiation of therapy. The median time to onset is 11 days, but symptoms can start on the first day and have been reported up to 318 days later. ABC HSR has occurred in patients who interrupted therapy without having had hypersensitivity and subsequently restart, but this is believed to be rare.[11,21] A single case of ABC HSR after switching from twice daily to once daily administration has also been reported.[22] Vigilance for the duration of ABC exposure is required.

The ABC HSR is a multi-organ process manifesting signs or symptoms from at least two of the following groups:

- **Fever** is the most common manifestation of ABC HSR, occurring in 80% of cases. Chills have been reported to accompany fever.
- **Rash** is experienced by 70% of cases, and pruritus can also occur. In contrast to the rash caused by non-NRTIs and sulphonamides, it is often mild and may go unnoticed by patients. When rash occurs in the absence of other features of HSR, ABC should not be discontinued.
- **Gastro-intestinal symptoms** such as nausea, vomiting, diarrhoea and abdominal pain are all features of HSR but may also occur in the absence of HSR, particularly when ABC is used with ZDV. Therefore, as with rash, patients with isolated gastro-intestinal symptoms should not discontinue ABC but should be followed up closely.
- **Constitutional symptoms** include fatigue, myalgias and generalised malaise.
- **Respiratory symptoms** occur in 18% of cases and include dyspnoea, cough and pharyngitis. Symptoms may be difficult to distinguish from those caused by influenza and other respiratory viruses. Respiratory symptoms together with abdominal symptoms suggest HSR rather than influenza or other respiratory illness.[23]

Clusters and combinations of symptoms are important in the diagnosis of ABC HSR. Table I illustrates the frequency of some combinations.[11,24]

TABLE I. FREQUENCY OF SYMPTOM COMBINATIONS IN ABACAVIR HYPERSENSITIVITY (ADAPTED FROM CLAY[24])

Systems and combinations	%
3 or 4 organ systems	49
Fever and rash	20
Fever and GIT	8
Skin and GIT	3
Skin and constitutional	3
Other combinations	17

GIT = gastro-intestinal.

With ABC HSR, there is an accentuation of symptoms in the hours immediately after the dose and worsening of symptoms with each subsequent dose. A number of case reports illustrate the varied clinical presentation, with Kawasaki-like illness, prominent exanthema and even disseminated intravascular coagulation being seen.[25-29]

If ABC is not terminated, or if it is re-initiated after temporary cessation, the HSR will progress to hypotension, renal dysfunction, bronchospasm and ultimately death.[11]

Abnormal laboratory findings may include leucopenia, anaemia and thrombocytopenia, as well as elevations

in transaminases, urea, creatinine and lactate dehydrogenase (LDH). Eosinophilia is usually absent.[11] Patch testing is currently only a research tool.

Termination of therapy is followed by rapid improvement in the symptoms.

Rechallenging with ABC leads to anaphylaxis and should be avoided even in cases where there was diagnostic uncertainty.

In Table II we set out the features of the first 3 cases of suspected HSR seen at the Tygerberg Children's Hospital Family Clinic for HIV. Of note is that HSR was documented in children across the racial spectrum. In all patients there was progression of symptoms over time and in 1 case there was a clear increase in severity associated with dosing. All children had abdominal symptoms and nonspecific rash. In these cases, children were stable on other ART drugs as they had all switched to ABC because of d4T toxicity.

MANAGEMENT OF PATIENTS INITIATING ABC

On commencement of ABC, patients should be counselled in detail about the possible signs of HSR and be advised to contact their care provider should any occur. To avoid confusion, therapy should not be initiated in patients with intercurrent symptoms.
It is advisable for patients to discuss symptoms early with the clinician rather than terminating therapy without consultation. Where termination without consultation occurs, ABC cannot be reinitiated. Patients should also be made aware of the special 'patient alert card' that comes in the packaging. This card should be presented to any health care provider who sees the child, especially when care is not given by the usual provider. Providers at emergency facilities may be less familiar with this condition, and where possible contact information for the usual care provider should be supplied as well.

Deciding whether to terminate therapy in a patient with suggestive symptoms can be difficult given the very nonspecific nature of the presentation. A detailed medical history should be obtained. The following should be considered:

- When was ABC initiated? In the case of ABC HSR, usually within the past 6 weeks.
- Are two or more systems involved?
- Do the symptoms increase with each dose?
- Are the symptoms exacerbated just after the dose?
- Do the symptoms fit into the well-recognised clusters?
- What other medications/medication is the patient taking, and what was the timing of their initiation related to the ABC?

If patients present with mild symptoms and it is not clear whether symptoms are due to HSR, the clinician may consider allowing an additional dose. The patient should be able to report back, or hospitalisation may be required for observation. If symptoms worsen, ABC should be terminated immediately and permanently. If symptoms do not worsen, ABC can be carefully con-

TABLE II. CLINICAL FEATURES IN 3 CHILDREN DIAGNOSED WITH ABC HSR AT TYGERBERG CHILDREN'S HOSPITAL AFTER A SINGLE DRUG SUBSTITUTION OF STAVUDINE FOR LIPO-ATROPHY

	Case 1	Case 2	Case 3
Race	White	Coloured	Black
Age (years)	9	5	10
Gender	Female	Male	Male
Time to onset of symptoms	<1 day	9 days	2 months
Accentuation with dose	Yes	Uncertain	Uncertain
Increasing severity	Yes	Yes	Yes
Time after onset to presentation to TCH (days)	1	5	3
Fever	No	Yes	No
Rash	Blotchy, erythematous on neck and hands Papules on the trunk and left arm	Extensive maculopapular on trunk, arms and legs Exanthema in mouth Non-purulent conjunctivitis	Fine papular rash on the chest
Gastrointestinal	Loss of appetite Epigastric and right upper quadrant tenderness	Nausea Loose stools	Abdominal pain and tenderness Vomiting Loss of appetite
Constitutional	Myalgias Malaise	Lethargy	Weight loss (1 kg)
Respiratory	No	No	Cough Red throat
Number of systems affected	3	4	4
Time to resolution	48 hours	5 days	2 - 3 days
HLA-B*5701	Negative – tested after the HSR	Positive – tested after the HSR	Negative – tested after the HSR

tinued while other possible reasons for the patient's symptoms are investigated. When the diagnosis is thought to be clear or there is sufficient concern, ABC should be terminated immediately and permanently.

Hospitalisation and special investigations will depend on the severity of symptoms. Corticosteroids do not prevent or alter the natural history of ABC HSR.[30] The reaction usually improves within 48 hours.

CONCLUSION

Clinicians treating children need to be very aware of the usefulness of ABC. Although there is no information on the prevalence of either ABC hypersensitivity or HLA-B*5701 in South African children, available data suggest that black children are at lower risk than Caucasian children, with no data on children of mixed race. Although screening for HLA-B*5701 is recommended and will prevent cases, research is needed to assess its cost effectiveness in the South African public health setting.

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CHANGING ANTIRETROVIRAL THERAPY IN CHILDREN

Leon J Levin, *MB BCh, FCPaed (SA), DTM&H*
Head, Paediatric programmes, Right To Care

This article is an update of a similar article published in the November 2005 edition of this journal. The rapid pace of changes in this field necessitates this update. Alarming numbers of children are failing both first- and second-line antiretroviral therapy regimens in a very short space of time, underscoring the importance of adhering to the basic guiding principles of changing therapy outlined below.

An important maxim in treating patients with HIV is that the first regimen is your best chance for success. Get it right the first time. Recent data show that the response of children to antiretroviral therapy (ART) both overseas and locally has been phenomenal.[1-4] Nevertheless, inevitably, increasing numbers of children will require a second-line regimen. It is therefore important that we have an approach to changing therapy.

There are two main reasons for changing ART – toxicity or intolerance, and failure of the current regimen. Other reasons include poor adherence (often improved with alternative antiretrovirals (ARVs)) and emergence of more effective or safer regimens.

TOXICITY OR INTOLERANCE

See the Guidelines for Antiretroviral Therapy in Children, p. 32 of this issue. When a patient exhibits intolerance to or toxicity from a single drug, the offending drug can often be replaced, e.g. replacing zidovudine (AZT) with abacavir (ABC) for bone marrow toxicity caused by AZT. Rarely, a reduction in dosage may be considered as long as the reduced dose is still in the therapeutic range.

For severe toxicity such as lactic acidosis or ABC hypersensitivity reaction, all ART should be stopped until the patient recovers. Only then can one cautiously restart ART. The offending agent should be switched for one that does not cause the same reaction.

Please note: The recommendations given in this article are only a guide. There is no substitute for expert advice when changing ART. Please consult the SA HIV Clinicians Society or the author for a list of local and overseas experts willing to assist you.

FAILURE OF CURRENT REGIMEN

Ideally one should not change therapy on the basis of a single viral load (VL) or CD4 count.

Before changing ART, a thorough assessment of adherence issues should be made. Adherence is the most important factor determining the success of an ART regimen.[5-7] Adherence issues must be resolved before changing therapy.

The US Public Health Service Guidelines[8] lists three types of failure of an antiretroviral regimen – virological, immunological and clinical failure (Fig. 1).

Unfortunately there are few paediatric data on when to change ART. PENPACT1, a study in Europe and the USA, is comparing changing ART at a VL of 1 000 versus 30 000 copies/ml. Their results will be presented at the World AIDS Congress in 2010. The South African guidelines recommend changing regimens when the VL is repeatedly above 1 000 copies/ml. Some paediatric experts would not change the therapy until the VL was repeatedly >5 000 - 10 000 copies/ml. Intervention does not necessarily mean a change of regimen. It may involve resolving adherence issues or changing to a holding strategy. With a persistently elevated VL, resistance mutations will accumulate[9] and cross-resistance to drugs that the patient has not been exposed to will occur.

Isolated VL 'blips', e.g. single levels of 50 - 1 000 copies/ml, are not usually associated with subsequent virological failure.[10,11] It is important to follow up a blip

Virological considerations:

Incomplete response to therapy:

- <10 × (1 $\log_{10}$) decrease from baseline VL at 8 - 12 weeks
- HIV RNA >400 copies/ml after 6 months or above the level of detection using an ultrasensitive assay after 12 months of therapy (some would accept a VL <5 000 copies/ml in a stable patient)

Viral rebound:

Repeated detection of plasma HIV RNA on ultrasensitive PCR assays where viral load was previously undetectable. Infrequent episodes of low level viraemia (<1 000 copies/ml) are common and not generally reflective of virological failure, whereas repeated or persistent viraemia (>1 000 copies/ml) more probably represents viral rebound (some would accept a VL <5 000 copies/ml in a stable patient)

Immunological considerations:

Incomplete immunological response to therapy:

- *<5 years of age:* Failure to improve CD4% values by ≥5% where CD4% was previously <15%
- *≥5 years of age:* Failure to improve CD4 values by ≥50 cells/µl above baseline where CD4 was previously <200 cells/µl within the first year of therapy

Immunological decline:

Sustained decline of 5% in CD4% below pre-therapy baseline at any age, or decline to below pre-therapy baseline in absolute CD4 cell count in children who are age 5 years and older

Clinical considerations:

Progressive neuro-developmental deterioration

Growth failure:

Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation

Severe or recurrent infection or illness:

Recurrence or persistence of AIDS-defining conditions or other serious infections

Fig. 1. Considerations for changing therapy in paediatric patients on antiretroviral therapy.[8]

with another VL after 3 months to exclude virological failure.

In children with low CD4 counts, an opportunistic infection can occur before the immune system has recovered and is not an indication to change ART. Similarly, with bronchiectasis recurrent lower respiratory tract infections are to be expected. Immune reconstitution inflammatory syndrome (IRIS) is also not an indication to change ART.

CHANGING THERAPY

DIFFERENT SCENARIOS WHEN CHANGING ART

There are three main scenarios when changing ART for drug failure.

- Early failure of a first regimen – there is unlikely to be much cross-resistance. A simple choice of a different regimen is usually adequate.
- Intermediate failure of a first regimen – some cross-resistance may be present. Genotyping may be helpful in ascertaining the degree of cross-resistance.
- Extensive prior treatment – extensive drug resistance is likely.

INITIAL ASSESSMENT

This is important in determining the cause of failure, as frequently the same issues will be a barrier to the success of a subsequent regimen.

Assessing adherence

Adherence is the most important factor in determining the success of an ART regimen.[5-7] Virological failure often follows poor adherence. Do not change therapy until the adherence issues have been resolved. Since the first regimen is often the best tolerated, subsequent regimens are often not as well tolerated and are likely to exacerbate adherence issues. Changing ART is never an emergency and is futile without addressing adherence. If adherence issues cannot be resolved quickly and you are worried about accumulating new resistance mutations, there may be a role for a 'holding strategy' until the family is ready to start the new regimen (see 'Holding strategies' below).

Exclude inadequate drug exposure

Possible causes include:

- Drug not being ingested, e.g. poor adherence, vomiting, or spitting up of an unpalatable drug such as ritonavir.
- Poor absorption, often in children with chronic diarrhoea or malabsorptive states.
- Increased drug metabolism – children beyond the neonatal age have markedly increased drug metabolism compared with adults. Post-marketing research often reveals package insert dosages to be inadequate. Consult an up-to-date paediatric ART guideline for correct dosages.
- Drug interactions – investigate all medications the patient is taking (including over-the-counter drugs and 'herbal' products) for possible drug interactions with ARV agents. Commonly implicated drugs include rifampicin, anti-epileptics, antimalarials and St John's wort.

Exclude other causes of a raised VL and/or a lower CD4 count

Intercurrent infections, opportunistic infections and immunisations may temporarily drop the CD4 count or raise the VL.

Ideally one should repeat the CD4 and VL 1 month later to ensure a return to baseline.

FACTORS TO CONSIDER WHEN CHANGING ANTIRETROVIRAL THERAPY

Expert advice

There is no substitute for expert advice when changing ART. The field is fraught with pitfalls for the unwary. Many patients' futures have been compromised by poor choices when changing therapy. There is always enough time to consult with an expert before changing therapy.

Resistance testing

Only genotypic assays are available in South Africa. Adult data reveal a short-term benefit of resistance testing in terms of virological response.[12,13] Paediatric data are conflicting,[14-17] but most experts believe that these assays have a role in changing ART in the face of resistance. Overseas guidelines recommend using resistance testing with every change of ART regimen caused by treatment failure.[8,18] This is also the recommendation of the SA HIV Clinicians Society, but prohibitive cost (over R4 000) will probably mean that in the South African state sector genotyping will only be done (if at all) after failure of a second regimen. Apart from the cost, genotyping has other limitations, including the following:

- Genotyping will only give information about the current regimen. If a patient has failed a drug in a previous regimen, genotyping may therefore falsely report susceptibility to that drug.
- Genotyping should be done while the patient is still taking their 'failing' regimen or within 4 weeks of stopping it.[18]
- Genotyping needs expert interpretation. It requires in-depth analysis by someone highly experienced in the field who also has all the details of the patient's treatment history. Knowledge of paediatric data and formulations are essential for correct advice.

At least 2 new drugs

Always try to include at least 2 (preferably 3) new or active agents.[18] One needs to be aware of cross-resistance (see below), since what may look like a 'new agent' may be ineffective as the virus is already resistant to it. Genotyping may help to select which drugs in the present regimen could be re-used. This does not apply to drugs in a *previous* regimen, as resistance mutations may be below the level of detection.

Preferably a new drug class

Studies have shown that the success of a subsequent regimen is increased if it contains an antiretroviral class to which the patient has not previously been exposed.[19,20] Two new drug classes, integrase and CCR5 inhibitors, should be available locally soon. They will be useful in highly experienced patients.

Do not add one drug to a failing regimen

Adding one drug to a failing regimen will predispose to the rapid development of resistance. This is the equivalent of monotherapy, which should generally be avoided at all costs. A variant of this is combining an active drug with a low genetic threshold for resistance, such as a non-nucleoside reverse transcriptase inhibitor (NNRTI) or raltegravir (integrase inhibitor), with 2 partially active drugs – in this situation the active drug will fail quickly.

Consider cross-resistance

Cross-resistance can be defined as phenotypic resistance to one drug resulting from mutations (genotypic) selected by another drug.[21] There is no cross-resistance between the different ARV classes. In the nucleoside reverse transcriptase inhibitor (NRTI) class, AZT and stavudine (d4T) are both thymidine analogues that select for the same resistance mutations, and there is cross-resistance between them. Generally, however, there is unlikely to be much NRTI cross-resistance after failing a first regimen.[21] With the currently available NNRTIs, on the other hand, there is a high level of cross-resistance. If a patient fails nevirapine (NVP), there will be high-level resistance to efavirenz (EFV). The new second-generation NNRTI etravirine (ETR), which will soon be available in South Africa, needs a few NNRTI mutations before there is high-level resistance against it. Unfortunately,

genotyping is necessary to ascertain whether ETR will be active after failing an NNRTI.

Cross-resistance in the protease inhibitors (PIs) depends on the PI concerned. Some PIs, e.g. atazanavir, amprenavir and nelfinavir, develop specific primary mutations first without conferring cross-resistance to other PIs. Secondary mutations conferring cross-resistance to other PIs will only occur after prolonged non-suppressive therapy.

Genotyping may help to clarify whether cross-resistance is present. Expert advice can be invaluable in this situation.

Consider drugs used for prevention of mother-to-child transmission (PMTCT)

Numerous studies have demonstrated resistance to NVP where mothers and their babies each receive one dose of NVP. There are emerging data in adults and infants suggesting reduced efficacy of future first-generation NNRTI-containing regimens.[22-24] It is therefore advisable to avoid NVP and EFV as part of first-line therapy in this situation. Consult the Guidelines for Antiretroviral Therapy in Children (p. 32 of this issue) when other ARVs have been used for prophylaxis.

Consider adding 3TC where M184V mutation present to maintain M184V mutation

Resistant HIV-1 with the hallmark 3TC resistance mutation, M184V, has reduced viral fitness, i.e. it replicates at a reduced rate and may reverse resistance to AZT, d4T and tenofovir (TDF). Therefore there may be value in adding in 3TC for salvage despite documented resistance.

However, the data are conflicting.[25,26] ABC will also maintain the M184V mutation without adding in 3TC (personal communication, Professor Mark Wainberg).

Pharmacokinetic enhancement

Where a single PI has been used previously, there may be a place for using a 'boosted PI', i.e. adding a small dose of ritonavir to the PI to inhibit the enzyme cytochrome P450 3A4, thus resulting in much higher levels of the PI. This may overcome minor degrees of PI resistance. Generally, however, it is advisable to only use boosted PI regimens.

Therapeutic drug monitoring (TDM)

TDM is still largely experimental in ART. However, there may be a place for TDM in salvage therapy with multiple drugs and multiple possible interactions. Contact the SA HIV Clinicians Society.

Dual PIs

This used to be quite 'fashionable' as a salvage therapy a few years ago. Invariably these children will have extremely high cholesterol and triglyceride levels. With the advent of newer agents and with data suggesting that dual PIs are no more efficacious than one boosted PI, this approach has become less popular.[27,28]

Mega- or giga-HAART

There are some adult data on empiric multidrug regimens,[29,30] but these are complex and poorly tolerated, and often with unfavourable drug interactions. With the advent of newer ARVs these regimens are no longer used much. A feeding gastrostomy tube may be used to simplify the administration of multiple medications.[31]

New ARVs

Several new agents are already available overseas with activity against resistant virus. TDF is available in South Africa, but it is not used routinely in children because of osteopenia and nephrotoxicity. However, if properly monitored TDF has some merit as a salvage drug in older patients. New PIs such as darunavir[32] and tipranavir[33] have revolutionised the management of highly resistant patients overseas. Raltegravir will be the first integrase inhibitor to be launched in South Africa. This potent and well-tolerated agent has shown phenomenal results in both naïve and ART-experienced adults.[34,35] Paediatric studies are ongoing.[36]

Etravirine, the second-generation NNRTI, may still be active in the face of resistance to first-line NNRTIs.[37,38] The CCR5 inhibitor maraviroc will probably have limited use in South Africa since it is only effective in patients who are CCR5-tropic and requires an expensive tropism assay prior to initiation.[39]

These new agents have achieved undetectable VLs in heavily ARV-experienced adults in contrast to earlier salvage regimens. Paediatric dosages and formulations are in development. Nevertheless, one can obtain Section 21 authorisation from the Medicines Control Council. Consult an expert.

Holding strategies

Not uncommonly one encounters a situation where a child needs to change ART but for various reasons is unable to. Common situations are unresolved adherence issues, inability to swallow tablets, or needing a new ARV that lacks paediatric dosing data or formulations. If the CD4 count is not too low, there may be place for a 'holding strategy'. These are only temporary solutions and do not replace a **suppressive regimen.** Holding strategies include **structured treatment interruptions, 3TC monotherapy and holding regimens.** These approaches should only be used on the advice of an expert.

- ***Structured treatment interruptions (STIs)***

There are three scenarios where one might consider stopping therapy:

Infants. Since paediatric HIV infection occurs with an immature immune system, treating with ARVs may allow the immune system to mature. Thus, a baby who has had several months of ART and is now over 1 year of age may cope without ART for several years because the immune system is now mature enough to cope with the baby's own HIV virus. The CHER study is currently looking at this phenomenon. Until the results of this study are published, this is not recommended as a routine practice.

Infants and children with immune reconstitution. This is a situation where the patient's CD4 count has recovered but the child is now virologically failing the current regimen. In this situation, there may be a place for taking the child off all therapy and watching the CD4 count carefully. Once the CD4 count drops below the criteria for starting ART, a new regimen can be started. The SMART study, in adults, showed a worse outcome in patients who stopped their ART compared with those who remained on ART,[40] but there are few paediatric data. PENTA11, a pilot interruption study in children, showed no deaths or serious clinical events on interruption for up to 48 weeks.[41]

Multidrug-experienced children with low CD4 counts. Adult data reveal that there is no place for STIs in a salvage situation.[42-44] The CD4 count drops rapidly and the patients are at risk for opportunistic infection.

3TC monotherapy

Although there are comparatively few adult data on this approach, 3TC monotherapy has gained popularity. There are data to suggest that giving 3TC monotherapy in patients failing multiple drugs results in slower disease progression than no therapy at all[45] because of reduced viral fitness in virus with the M184V mutation. This can be attempted. The approach may have merit in patients failing 3TC but with good CD4 counts and unable to start a definitive suppressive regimen. 3TC monotherapy should be avoided in patients who have ever had a very low CD4 count (low CD4 nadir). When the CD4 drops or symptoms develop, the child should be placed on a fully suppressive regimen.

Holding or bridging regimens

These are simplified regimens, usually consisting of 3 or 4 NRTIs with the purpose of maintaining resistance mutations so that the virus has a reduced replicative ability. The aim once again is to 'buy time' for the child who is unable to start a definitive suppressive regimen. A suitable child would be one with extensive NRTI resistance but in whom you would not want to develop more PI or NNRTI resistance. Therefore future options are preserved. Since there is already extensive NRTI resistance, there is no worry that the child will develop more resistance to the NRTIs. In adults, AZT/3TC/ABC/TDF has been used.[46] In younger children, TDF can be omitted. Once again this approach is inappropriate for patients with a very low CD4 count. Once the CD4 count drops or symptoms develop the child should be placed on a fully suppressive regimen.

Quality of life in end-stage disease

In patients without further ARV options and who are failing or not tolerating mega-HAART, there may be a place for reducing the number of drugs to make life more tolerable. The disease will still progress more slowly than if off ARVs. Consult an expert to reduce the number of agents to a more tolerable regimen. 3TC should always be included in such a regimen. As more new drugs become available, this scenario is becoming less common.

CONCLUSION

Changing ART is a highly complex field, which can have major impact on a child's future if done incorrectly. It is therefore strongly recommended that an expert be consulted before changing any child's ART. This would apply equally to a child failing their first regimen. However, the future is rosy with wonderful new antiretroviral options and certainly something worth looking forward to.

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CONFERENCE REPORT

PAEDIATRIC OVERVIEW, IAS2009

Polly Clayden
HIV i-Base, UK

A wealth of paediatric data was presented at IAS 2009. Also preceding the conference was the 1st International Workshop on HIV Pediatrics, which looks as if it will become an annual fixture on the conference calendar and gave an additional opportunity to present and discuss the state of the art in the field.

Overall, far too much was presented to review here. Abstracts, some slides and, for IAS2009, webcasts can be viewed on the respective conference websites. We have also covered some paediatric cohorts and a few studies in more detail in our review of programme data in *HTB South*, distributed with the *Journal*.

Several themes occurred over and over again at both meetings.

National capacity for early infant diagnosis, which not only enables early initiation of treatment but also gives a clearer picture of how well prevention of mother-to-child transmission (PMTCT) programmes are performing, with the goal of vastly reducing cases of paediatric HIV, is not yet nearly sufficient in most places.

Where infants are diagnosed in time, early initiation of treatment is not without its difficulties. It can, however, be extremely beneficial in young children.

Treatment of children who are HIV-infected despite exposure to single-dose nevirapine through PMTCT is another challenge, as is what to do in the longer term with exposed children initiated on a protease inhibitor-containing HAART to overcome the risks of NNRTI resistance.

Strategies to simplify regimens, including paediatric fixed-dose combinations and once-a-day dosing, are essential for successful management of children with HIV, as are strategies to enable co-treatment of tuberculosis in this population.

The research summarised below addresses these issues.

EARLY INFANT DIAGNOSIS

Several guidelines now recommend universal treatment for HIV-infected infants. However, in resource-limited settings early infant diagnosis (EID) is frequently an obstacle to early initiation of antiretrovirals.

A survey by World Health Organization (WHO) asked, 'What is available for early infant diagnosis?' and found the number of laboratories in several countries mismatched to the estimated number of HIV-exposed infants and necessary tests. This assessment of national capacity was conducted to inform revisions to their guidelines for infant diagnosis and treatment.[1]

For this survey, a questionnaire on clinical and laboratory capacity was sent to HIV experts in 34 high-burden countries and data were collected between February and April 2008. Replies were received from 18 of the 34 selected countries: 12 African, two South American, two Asian and one Middle Eastern.

This revealed huge variation in the number of children assessed per laboratory (range 7 - 190 000 during the study period). When virological tests were offered, the entry points were usually inpatient/outpatient services, prevention of mother-to-child transmission (PMTCT) or antiretroviral therapy (ART) sites, and laboratories were centralised and usually located in capital cities. Six countries surveyed implement HIV DNA polymerase chain reaction (PCR), 5 RNA PCR and 7 both. Ten countries used filter paper with dried blood spots (DBS) to transport samples. All the countries that responded had capacity to measure CD4% and absolute CD4 cell counts.

Although the survey confirmed that several high-burden countries are building capacity for EID, it showed that at present in many countries capacity does not reflect estimated need.

In many resource-limited countries it is only possible to use a single diagnostic test. The optimal time to per-

form this is unclear, however, particularly when children are breastfed. The WHO researchers used a model to calculate the number of children becoming infected and being diagnosed at different time points from birth in order to estimate the optimal time to diagnose the maximum number of children but at the same time minimise mortality.[2]

This modelling showed a decreasing trend of infant survival at 6 months, depending on the time the test was performed. The investigators suggested that 4 - 6 weeks of age is the optimal time for infant testing in a breastfeeding population.

With greater laboratory capacity and newer technology, testing earlier than 6 weeks could mean earlier initiation of treatment. But the sensitivity of viral detection tests before 6 weeks of age is unknown, particularly when performed on infants with antiretroviral exposure for PMTCT.

A South African study looked at the sensitivity of assays at earlier time points in infants born to HIV-positive women at Rahima Moosa Hospital, Johannesburg.[3] Blood was sampled at birth and at 2, 4, 6 and 10 weeks, and stored. HIV-exposed infants were routinely tested at 6 weeks with HIV DNA PCR using a liquid blood sample. Stored DBS samples from each time point were tested with HIV DNA PCR (Amplicor v1.5), TaqMan HIV-1 (CAP/CTM) and APTIMA HIV-1 (GEN-PROBE) assays. The investigators used samples from two age-matched, PCR-negative infants as controls.

Mothers received a range of PMTCT interventions: no antiretrovirals, single-dose nevirapine (NVP), single-dose NVP plus zidovudine (AZT) or HAART.

At 9 months of the study, 253/373 (68%) infants had 6-week PCR results; the remaining 120 (32%) did not return for testing. Eighteen (7.1%) were HIV infected at 6 weeks despite the majority receiving formula milk exclusively and all receiving NVP and AZT PMTCT prophylaxis. Of the 17 infected infants with complete results, both CAP/CTM and APTIMA assays were positive in 11/17, 13/13 and 14/14 birth, 4- and 6-week samples, respectively.

The quantitative CAP/CTM assay showed lower viral load results at 2 weeks of age (the only time point when false negatives occurred). The investigators noted that this was probably due to PMTCT prophylaxis increasing the proportional number of infants infected *in utero* who can therefore be diagnosed at birth.

Both assays were more sensitive for earlier HIV detection than HIV DNA PCR, which detected 9/17 birth samples. CAP/CTM had the highest specificity (100%) and HIV DNA PCR the lowest (95%).

Although this is a small sample, newer technologies appear to be more sensitive than standard PCR. These initial results suggest that the majority of *in utero* and perinatal infections can be detected by using either CAP/CTM or APTIMA assays if they are available.

There were also reports from programmes using DBS.

A sub-study of the PMTCT Keso Bora trial conducted in Burkina Faso used a quantitative HIV RNA assay (Biocentric) and assessed DBS samples compared with paired plasma samples obtained from HIV-exposed infants aged up to 6 weeks, 3 - 6 months and 9 - 18 months.[4] All measurements were performed locally.

The study investigators reported 100% sensitivity (102/102) and specificity (105/105) (95% confidence interval (CI) 97.2 - 100%, correlation 0.906) using DBS. (Of note: Biocentric is the homebrew ANRS assay, so they would have to develop their own probes, reagents, etc.)

A Cambodian study assessed the feasibility of very early diagnosis (0 - 3 days of age) using heel-prick samples on DBS and a real time DNA assay (Bicentric).[5] A second DBS was performed at week 6. Infants with positive results at 0 - 3 days or 6 weeks were followed up with HIV RNA quantification as soon as possible. At 0 - 3 days, 3/370 (0.8%) infants had positive results (1 infant died before week 6). 327/333 were confirmed negative at 6 weeks and 6 were DNA positive (1.8%) and subsequently confirmed RNA positive.

The investigators suggested that these preliminary results demonstrate the feasibility of a minimally invasive very early diagnosis using DBS.

DIFFICULTIES WITH IMPLEMENTATION

A study from Swaziland, conducted by the national ART programme and the Clinton Foundation, highlighted the difficulties of treatment initiation in infants following early diagnosis.[6]

Since March 2007 the EID programme using DNA PCR was expanded in response to high infant mortality in HIV-infected children. By November 2008, however, this had led to neither an increase in infants receiving treatment nor a decrease in mortality.

The study was a retrospective record review of all infants testing positive at 15 health facilities in the Manzini Region from January to August 2008. The investigators reported that 78% of results were available at the facility, and 44% of results were documented as having been received by the caregiver. Only 58/176 (33%) of children were enrolled at an ART centre and 34 initiated on treatment. Of those with data available

81% were eligible for ART, and among eligible children, 82% initiated treatment. Overall 19% of infants testing positive were initiated on treatment at the time of the evaluation.

This study found that the greatest points of loss are return of the result to caregivers and infant enrolment at the ART centre for treatment.

INFANT OUTCOMES

There are limited data describing outcomes for infants initiating treatment at less than 1 year.

The MTCT Plus Initiative showed data from sites in eight African countries and Thailand comparing infants with older children initiated between February 2003 and September 2008.[7] The investigators looked at change in CD4 percentage from baseline using linear modelling adjusted for duration of highly active antiretroviral therapy (HAART), country, baseline CD4 percentage, NVP exposure for PMTCT, and age at initiation.

Of 542 children initiating treatment and followed up for a median of 30 months (intraquartile range (IQR) 12 - 39), 190 (35%) were aged <12 months at initiation and the remainder >12 months (median 36 months, IQR 19.5 - 67), 51% were male, and18% had Centers for Disease Control (CDC) stage C disease. The infants had a higher mortality rate than the older children, 7.5 v. 3.2/100 person-years. Of 31 (54%) infant deaths, 81% occurred within 3 months of treatment initiation.

Among the children for whom data were available there was no difference between infants and older children in change of CD4 percentage from baseline. Baseline CD4 percentage ($p<0.01$) and time on HAART ($p<0.001$) were significantly associated with an increase in CD4 percentage in multivariate analysis.

In this analysis, although infants initiating HAART had a higher mortality at the start of treatment, the infants who survived had good immunological response over >3 years of follow-up, similar to that of older children.

A South African review of infants initiated on HAART at the Family Clinic for HIV at Tygerberg Hospital and Ikwezi community clinic from June 2007 to August 2008 showed high levels of virological suppression to 24 weeks.[8] Infants received lopinavir/ritonavir (LPV/r) with stavudine (d4T) and lamivudine (3TC) in accordance with South African guidelines. Of 98 initiated, 47 had 24 weeks of follow-up. Of the remainder, 6 (6%) were lost to follow-up, 6 (6%) died and 33 (33.7%) were transferred. The median age at initiation was 4.5 months and 33 (70%) infants were ≤6 months old (median age 3.68 months). All had immunological or clinical criteria for treatment. The majority, 42/47 (89.4%) of all infants and 30/33 (91%) ≤6 months of age, had WHO stage 3 or 4 disease.

Tuberculosis (TB) is a common co-morbidity in this population, and 11/47 infants required co-therapy with rifampicin (given with additional ritonavir). At 24 weeks 37/47 children (78.7%) in the >6 months age group and 26/33 (81.8%) aged <6 months had viral loads <50 copies/ml.

The investigators noted that the low age of initiation of treatment in this cohort reflected young infants with severe HIV disease rather than early initiation of treatment to prevent mortality and morbidity.

IMPROVED NEURODEVELOPMENTAL OUTCOMES

The developing brain is a major target for HIV. It is not yet known whether timing of initiation of antiretroviral therapy will affect neurodevelopmental outcomes in infants.

A substudy of CHER compared neurodevelopmental outcomes of 115 infants in this study from Tygerberg Children's Hospital with 84 control infants enrolled in a linked vaccine study, CIPRA-SA Project4.[9]

In this prospective study, the investigators looked at the neurodevelopmental profile, according to the Griffiths Mental Developmental Scales (GMDS), at 10 - 15 months of age in four groups of infants:

- HIV-unexposed, uninfected
- HIV-exposed, uninfected
- HIV-infected, HAART initiated before 12 weeks of age
- HIV infected, HAART deferred until eligibility criteria met.

The investigators were blinded to the infants' groups and a translator was used for Xhosa-speaking participants. Of 115 infants from CHER enrolled, 13 withdrew from the study and/or were not co-enrolled (10 early, 3 deferred), 8 died (all deferred) and 4 were excluded (3 early, 1 deferred).

The investigators found that infants initiated on early ART have significantly better locomotor and general scores on the GMDS at a median age of 11 months compared with infants on deferred HAART. Although mean quotients were lower on the other subscales in the deferred group, the differences were not significant. The mean scores on all subscales in the unexposed, uninfected group and the early HAART group were similar. They noted these results were 'despite careful monitoring and ready access to ART in the latter' (Table I).

TABLE I. MEAN QUOTIENTS OF INFANTS FOR DEFERRED V. EARLY HAART AND HIV-EXPOSED UNINFECTED AND UNEXPOSED INFANTS

	Deferred ART	Early ART	HIV-exposed uninfected	HIV-unexposed	*p*-value early v. deferred
No. assessed	26	66	28	34	
Median age in months (range)	11.0 (10.1 - 14.4)	11.0 (10.0 - 15.5)	11.4 (10.1 - 15.5)	11.5 (9.9 - 13.6)	
Mean locomotor quotient ± 1 SD	88.9±16.3	97.6±12.5	105.3±14.3	101.6±3.7	0.01
Mean general quotient ± 1 SD	100.1±13.8	106.3±10.6	106.0±10.1	106.9±11.7	0.02

TREATING CHILDREN EXPOSED TO SINGLE-DOSE NEVIRAPINE FOR PMTCT

Two studies looked at treatment of HIV-infected children with prior exposure to NVP to prevent MTCT.

Preliminary findings from IMPAACT 1060 confirmed concerns that NVP-exposed children could do less well receiving NVP containing HAART than protease inhibitor (PI)-containing HAART.[10,11]

This was a randomised trial of treatment-eligible children aged 6 months - 3 years conducted in seven African countries. NVP-exposed (cohort 1, *N*=288) and unexposed (cohort 2, *N*=288) children received either LPV/r or NVP plus 3TC and AZT. Children were stratified by age <12 months v. ≥12 months with an equal number to be enrolled in each age group.

A similar study of exposed and unexposed mothers had also been conducted (A5208). In this trial, the arm in which exposed mothers received NVP-containing HAART was stopped early by the Data Safety Monitoring Board (DSMB) owing to superior performance of the LPV/r-containing HAART arm.[12,13]

Following a scheduled DSMB review of IMPAACT 1060 on 20 April 2009, enrolment to cohort 1 also closed prematurely owing to a trend towards consistency with the A5208 results. At 24 weeks, virological failure (<400 copies/ml) was observed in 40% of the 60 infants <12 months v. 23% ≥12 months receiving NVP and LPV/r, respectively. Among the older children, 29% out of 22 and 17% of 19 receiving NVP and LPV/r experienced failure.

Several guidelines already recommend using LPV/r-based treatment for single-dose NVP-exposed infants. The NEVEREST study investigated whether NVP-exposed children, initially suppressed on LPV/r-based HAART, can safely switch to a NVP-based regimen.[14,15]

In this study children aged 6 weeks - 2 years and eligible for treatment (*N*=323) were initiated on LPV/r plus 3TC and d4T. Children achieving a viral load <400 copies/ml and stable for ≥3 months were randomised (*N*=195) to either remain on LPV/r (control, *N*=99) or switch to NVP (switch, *N*=96), and then followed up to 52 weeks.

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

They suggested that poorer adherence in the control group, due to the unpleasantness in taste of LPV/r syrup, may have led to more blipping and, in turn, unsustained viral suppression to 50 copies/ml during follow-up. In contrast, when they looked at sustained suppression to <1 000 copies/ml, 98% v. 80% of children in the control and switch groups achieved this (*p*=0.001). The investigators suggest that this study provides proof of concept that re-use of NVP is possible under some circumstances for HIV-infected children exposed to NVP prophylaxis and should be further investigated. They note that the clinical significance of low-level viraemia in the control group needs further study.

This group also showed data from an evaluation of lipid profiles in children in the control and switch groups.[16] They found no difference between the two groups at randomisation. But at 9 months after the change in regimen non-fasting total cholesterol (TC) and high-density lipoprotein (HDL) were significantly higher among the switch group (mean TC 4.13, HDL 1.36 mmol/l) compared with the control group (mean TC 3.73, HDL 1.07 mmol/l). Significantly lower triglyceride (TG) levels were found in the switch group (mean TG 1.36 mmol/l) compared with the control group (mean TG 1.53 mmol/l). They noted that the clinical significance of these non-fasting lipid changes requires further investigation.

Switching may provide a promising option for children originally initiated on PI-based HAART to preserve second-line options. At this stage, switching requires close virological monitoring after the switch in order to be done safely.

Another NEVEREST trial of efavirenz (EFV) v. LPV/r is planned in NVP-exposed children >3 years old.

These studies all underscore the limited treatment options available for children, particularly in resource-limited settings.

USING A NEVIRAPINE-CONTAINING FIXED-DOSE COMBINATION IN THE CHAPAS TRIAL

Paediatric fixed-dose combination (FDC) tablets provide simpler alternatives to liquids for children.

Cipla have produced scored, dispersible tablets of d4T/3TC/NVP (baby and junior Triomune) with the correct dose ratios for children.

A sub-study of the CHAPAS trial (Children with HIV in Africa Pharmacokinetics and Adherence of Simple Antiretroviral Regimens), in Zambia, evaluated the need for dose escalation of NVP.[17] This strategy is currently recommended but requires dosing with separate tablets, making initial treatment more complex.

Children were randomised to start antiretroviral therapy with full-dose nevirapine (Triomune a.m./p.m.) v. dose escalation, using an initial 14 days of half-dose NVP (Triomune a.m.; Lamivir-S (combined d4T/3TC) p.m.) followed by full dose. Children were dosed in accordance with WHO weight band tables. The primary endpoint was clinical/laboratory grade 3/4 adverse events (AEs) related to NVP.

In this comparison, 211 children aged 2 - 9 years with a median CD4 percentage of 13% were followed for a median of 92 weeks. Severe stunting, wasting and immunosuppression were common in the children. Seventeen children were lost to follow-up.

The investigators reported 31 (18 per 100 person-years) v. 29 (16.5 per 100 person-years) grade 3/4 AEs definitely/probably or uncertainly NVP-related in children receiving full-dose v. dose-escalation (incidence rate ratio (IRR) 1.09 (95% CI 0.63 - 1.87), p=0.74).

Twelve (11%) full-dose v. 2 (2%) dose escalation children had grade 2 disseminated skin rash and 1 receiving full dose had grade 1 rash. Two children (one from each arm) substituted with EFV; 3 continued full-dose NVP; 9 (8 full dose and 1 dose escalation) stopped NVP and restarted with successful dose escalation; and 1 full dose stopped, started a lower NVP dose, had another rash and substituted EFV.

Overall 90% of children who started with full-dose NVP continued uninterrupted in this study. As dose escalation requires provision of separate drug formulations, the evaluation of policy implications for dose escalation of NVP in fixed-dose combination HAART is ongoing.

The CHAPAS trial also investigated the pharmacokinetics of NVP in children treated with Triomune Baby/Junior and rifampicin-based TB treatment.[18]

EFV-based regimens are currently recommended for concomitant use with rifampicin, but EFV is not currently indicated for children below 3 years of age. Earlier CHAPAS data suggest that the higher dose ratio of NVP to NRTI in Triomune Baby/Junior may compensate for the dose reduction induced by rifampicin.

Pharmacokinetic sampling was performed in 22 children after 4 weeks of concurrent NVP and rifampicin-containing regimens. Rifampicin was dosed at 10 - 20 mg/kg per day. Samples were pre-dose (C_0) and 1, 2 and 6 hours post-dose, and NVP plasma concentrations were determined using LC-MS/MS. NVP pharmacokinetics in children without TB treatment (N=16) were compared in multivariate linear regression analysis. The median age of the 21 children analysed was 1.55 (range 0.66 - 3.18) years, and 10 were girls.

The investigators found that only 11 (52%) of the children receiving TB treatment reached sufficient NVP trough levels (C_0 <3.0 mg/l). Multivariate analysis revealed a 41% (95% CI 24 - 55%) reduction in NVP AUC with concomitant rifampicin. They noted a 3.4% increase in AUC for each 10 mg/m^2 increase in NVP dose/m^2.

They recommend caution with this approach in young children until more efficacy and safety data are available. They suggest that an increased NVP dose is likely to be necessary and requires further evaluation.

ONCE-A-DAY LAMIVUDINE AND ABACAVIR, AND ABACAVIR HYPERSENSITIVITY IN THE ARROW TRIAL

Simplification of HAART regimens provides benefit for children, caregivers and health workers. To date there are no data on once-daily use of 3TC and abacavir (ABC) in resource-limited settings.

A substudy from the ARROW trial (a randomised trial of monitoring and first-line induction-maintenance strategies) compared the PK of once- v. twice-daily 3TC and abacavir (ABC) (Kivexa).[19] This was a cross-over study performed in 41 Ugandan children aged 3 - 12 years receiving HAART, dosed according to weight bands. The ARROW trial uses scored tablets of ABC/3TC to ensure better accuracy of division and more flexible dosing. Total daily doses were 150+300 mg, 225+450 mg and 300+600 mg for children weighing 12 - 20 kg, 20 - 25 kg and >25 kg, respectively.

PK sampling was performed for twice-daily dosing at steady state (36 weeks) pre-dose, and 1, 2, 4, 6, 8 and 12 hours post dose. Children were then switched to the once-daily dose and further sampling was performed at 4 weeks with an additional sampling at 24 hours. Daily area under the curve (AUC_{0-24}) and peak level (C_{max}) were compared by geometric mean ratios (GMR). GMR with 90% CI within 0.80 - 1.25 was considered to be bioequivalent. PK parameters were available for 35 and 36 children for 3TC and ABC, respectively. Approximately half were in the younger age group.

The investigators reported that in children 3 - 12 years, AUC_{0-24} of both 3TC and ABC were bioequivalent with once and twice-daily regimens but C_{max} was 76% and 64% higher for 3TC and ABC respectively. No grade 3/4 adverse events were reported and no child discontinued after the switch to once-daily dosing.

In this analysis, in contrast to data from European children in PENTA 13, 3TC AUC levels in 3 - 6- and 7 - 12-year-old children were similar for both once- and twice-daily dosing and similar to levels in older children. The investigators noted that many younger children in PENTA 13, whose 3TC levels were lower, received syrups, but ARROW children received tablets. They concluded that these results suggest that once-daily dosing of 3TC and ABC is feasible in resource-limited settings.

The ARROW investigators also showed data describing successful management of hypersensitivity reactions among children in this trial in Uganda and Zimbabwe.[20]

The WHO recommends ABC for paediatric first-line treatment. Hypersensitivity reactions (HSR) occur in 2 - 5% of people receiving ABC in clinical trials and are strongly associated with the presence of the HLA-B*5701 allele. Prospective screening for HLA-B*5701 is sometimes recommended, but this pharmacogenetic test is rarely available in resource-limited settings.

Clinical diagnosis and management may be complicated in this setting due to widespread use of NVP and co-trimoxazole and febrile infections.
Health workers and caregivers were trained in recognition and management of ABC-HSR and all suspected HSR underwent independent clinical review. ABC was only discontinued in 7 cases.

The investigators reported that suspected ABC-HSR was rare (3/1 207, 0.2% (95% CI, 0.05 - 0.7%)) in this trial, consistent with reports of a lower prevalence of HLA-B*5701 in black populations. Clinical symptoms (fever, rash) occurred 9 - 13 days after initiation of HAART; 2/3 cases had additional gastro-intestinal and respiratory symptoms and required hospitalisation.

ABC-HSR was successfully managed despite co-administration of co-trimoxazole and NVP, and the investigators recommend that ABC can be used safely in resource-limited settings.

All references from 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 19 - 22 July 2009, Cape Town, unless otherwise stated.

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CONFERENCE REPORT

PAEDIATRIC OVERVIEW, IAS2009

Polly Clayden
HIV i-Base, UK

A wealth of paediatric data was presented at IAS 2009. Also preceding the conference was the 1st International Workshop on HIV Pediatrics, which looks as if it will become an annual fixture on the conference calendar and gave an additional opportunity to present and discuss the state of the art in the field.

Overall, far too much was presented to review here. Abstracts, some slides and, for IAS2009, webcasts can be viewed on the respective conference websites. We have also covered some paediatric cohorts and a few studies in more detail in our review of programme data in *HTB South*, distributed with the *Journal*.

Several themes occurred over and over again at both meetings.

National capacity for early infant diagnosis, which not only enables early initiation of treatment but also gives a clearer picture of how well prevention of mother-to-child transmission (PMTCT) programmes are performing, with the goal of vastly reducing cases of paediatric HIV, is not yet nearly sufficient in most places.

Where infants are diagnosed in time, early initiation of treatment is not without its difficulties. It can, however, be extremely beneficial in young children.

Treatment of children who are HIV-infected despite exposure to single-dose nevirapine through PMTCT is another challenge, as is what to do in the longer term with exposed children initiated on a protease inhibitor-containing HAART to overcome the risks of NNRTI resistance.

Strategies to simplify regimens, including paediatric fixed-dose combinations and once-a-day dosing, are essential for successful management of children with HIV, as are strategies to enable co-treatment of tuberculosis in this population.

The research summarised below addresses these issues.

EARLY INFANT DIAGNOSIS

Several guidelines now recommend universal treatment for HIV-infected infants. However, in resource-limited settings early infant diagnosis (EID) is frequently an obstacle to early initiation of antiretrovirals.

A survey by World Health Organization (WHO) asked, 'What is available for early infant diagnosis?' and found the number of laboratories in several countries mismatched to the estimated number of HIV-exposed infants and necessary tests. This assessment of national capacity was conducted to inform revisions to their guidelines for infant diagnosis and treatment.[1]

For this survey, a questionnaire on clinical and laboratory capacity was sent to HIV experts in 34 high-burden countries and data were collected between February and April 2008. Replies were received from 18 of the 34 selected countries: 12 African, two South American, two Asian and one Middle Eastern.

This revealed huge variation in the number of children assessed per laboratory (range 7 - 190 000 during the study period). When virological tests were offered, the entry points were usually inpatient/outpatient services, prevention of mother-to-child transmission (PMTCT) or antiretroviral therapy (ART) sites, and laboratories were centralised and usually located in capital cities. Six countries surveyed implement HIV DNA polymerase chain reaction (PCR), 5 RNA PCR and 7 both. Ten countries used filter paper with dried blood spots (DBS) to transport samples. All the countries that responded had capacity to measure CD4% and absolute CD4 cell counts.

Although the survey confirmed that several high-burden countries are building capacity for EID, it showed that at present in many countries capacity does not reflect estimated need.

In many resource-limited countries it is only possible to use a single diagnostic test. The optimal time to per-

form this is unclear, however, particularly when children are breastfed. The WHO researchers used a model to calculate the number of children becoming infected and being diagnosed at different time points from birth in order to estimate the optimal time to diagnose the maximum number of children but at the same time minimise mortality.[2]

This modelling showed a decreasing trend of infant survival at 6 months, depending on the time the test was performed. The investigators suggested that 4 - 6 weeks of age is the optimal time for infant testing in a breastfeeding population.

With greater laboratory capacity and newer technology, testing earlier than 6 weeks could mean earlier initiation of treatment. But the sensitivity of viral detection tests before 6 weeks of age is unknown, particularly when performed on infants with antiretroviral exposure for PMTCT.

A South African study looked at the sensitivity of assays at earlier time points in infants born to HIV-positive women at Rahima Moosa Hospital, Johannesburg.[3] Blood was sampled at birth and at 2, 4, 6 and 10 weeks, and stored. HIV-exposed infants were routinely tested at 6 weeks with HIV DNA PCR using a liquid blood sample. Stored DBS samples from each time point were tested with HIV DNA PCR (Amplicor v1.5), TaqMan HIV-1 (CAP/CTM) and APTIMA HIV-1 (GEN-PROBE) assays. The investigators used samples from two age-matched, PCR-negative infants as controls.

Mothers received a range of PMTCT interventions: no antiretrovirals, single-dose nevirapine (NVP), single-dose NVP plus zidovudine (AZT) or HAART.

At 9 months of the study, 253/373 (68%) infants had 6-week PCR results; the remaining 120 (32%) did not return for testing. Eighteen (7.1%) were HIV infected at 6 weeks despite the majority receiving formula milk exclusively and all receiving NVP and AZT PMTCT prophylaxis. Of the 17 infected infants with complete results, both CAP/CTM and APTIMA assays were positive in 11/17, 13/13 and 14/14 birth, 4- and 6-week samples, respectively.

The quantitative CAP/CTM assay showed lower viral load results at 2 weeks of age (the only time point when false negatives occurred). The investigators noted that this was probably due to PMTCT prophylaxis increasing the proportional number of infants infected *in utero* who can therefore be diagnosed at birth.

Both assays were more sensitive for earlier HIV detection than HIV DNA PCR, which detected 9/17 birth samples. CAP/CTM had the highest specificity (100%) and HIV DNA PCR the lowest (95%).

Although this is a small sample, newer technologies appear to be more sensitive than standard PCR. These initial results suggest that the majority of *in utero* and perinatal infections can be detected by using either CAP/CTM or APTIMA assays if they are available.

There were also reports from programmes using DBS.

A sub-study of the PMTCT Keso Bora trial conducted in Burkina Faso used a quantitative HIV RNA assay (Biocentric) and assessed DBS samples compared with paired plasma samples obtained from HIV-exposed infants aged up to 6 weeks, 3 - 6 months and 9 - 18 months.[4] All measurements were performed locally.

The study investigators reported 100% sensitivity (102/102) and specificity (105/105) (95% confidence interval (CI) 97.2 - 100%, correlation 0.906) using DBS. (Of note: Biocentric is the homebrew ANRS assay, so they would have to develop their own probes, reagents, etc.)

A Cambodian study assessed the feasibility of very early diagnosis (0 - 3 days of age) using heel-prick samples on DBS and a real time DNA assay (Bicentric).[5] A second DBS was performed at week 6. Infants with positive results at 0 - 3 days or 6 weeks were followed up with HIV RNA quantification as soon as possible. At 0 - 3 days, 3/370 (0.8%) infants had positive results (1 infant died before week 6). 327/333 were confirmed negative at 6 weeks and 6 were DNA positive (1.8%) and subsequently confirmed RNA positive.

The investigators suggested that these preliminary results demonstrate the feasibility of a minimally invasive very early diagnosis using DBS.

DIFFICULTIES WITH IMPLEMENTATION

A study from Swaziland, conducted by the national ART programme and the Clinton Foundation, highlighted the difficulties of treatment initiation in infants following early diagnosis.[6]

Since March 2007 the EID programme using DNA PCR was expanded in response to high infant mortality in HIV-infected children. By November 2008, however, this had led to neither an increase in infants receiving treatment nor a decrease in mortality.

The study was a retrospective record review of all infants testing positive at 15 health facilities in the Manzini Region from January to August 2008. The investigators reported that 78% of results were available at the facility, and 44% of results were documented as having been received by the caregiver. Only 58/176 (33%) of children were enrolled at an ART centre and 34 initiated on treatment. Of those with data available

81% were eligible for ART, and among eligible children, 82% initiated treatment. Overall 19% of infants testing positive were initiated on treatment at the time of the evaluation.

This study found that the greatest points of loss are return of the result to caregivers and infant enrolment at the ART centre for treatment.

INFANT OUTCOMES

There are limited data describing outcomes for infants initiating treatment at less than 1 year.

The MTCT Plus Initiative showed data from sites in eight African countries and Thailand comparing infants with older children initiated between February 2003 and September 2008.[7] The investigators looked at change in CD4 percentage from baseline using linear modelling adjusted for duration of highly active antiretroviral therapy (HAART), country, baseline CD4 percentage, NVP exposure for PMTCT, and age at initiation.

Of 542 children initiating treatment and followed up for a median of 30 months (intraquartile range (IQR) 12 - 39), 190 (35%) were aged <12 months at initiation and the remainder >12 months (median 36 months, IQR 19.5 - 67), 51% were male, and18% had Centers for Disease Control (CDC) stage C disease. The infants had a higher mortality rate than the older children, 7.5 v. 3.2/100 person-years. Of 31 (54%) infant deaths, 81% occurred within 3 months of treatment initiation.

Among the children for whom data were available there was no difference between infants and older children in change of CD4 percentage from baseline. Baseline CD4 percentage ($p<0.01$) and time on HAART ($p<0.001$) were significantly associated with an increase in CD4 percentage in multivariate analysis.

In this analysis, although infants initiating HAART had a higher mortality at the start of treatment, the infants who survived had good immunological response over >3 years of follow-up, similar to that of older children.

A South African review of infants initiated on HAART at the Family Clinic for HIV at Tygerberg Hospital and Ikwezi community clinic from June 2007 to August 2008 showed high levels of virological suppression to 24 weeks.[8] Infants received lopinavir/ritonavir (LPV/r) with stavudine (d4T) and lamivudine (3TC) in accordance with South African guidelines. Of 98 initiated, 47 had 24 weeks of follow-up. Of the remainder, 6 (6%) were lost to follow-up, 6 (6%) died and 33 (33.7%) were transferred. The median age at initiation was 4.5 months and 33 (70%) infants were ≤6 months old (median age 3.68 months). All had immunological or clinical criteria for treatment. The majority, 42/47 (89.4%) of all infants and 30/33 (91%) ≤6 months of age, had WHO stage 3 or 4 disease.

Tuberculosis (TB) is a common co-morbidity in this population, and 11/47 infants required co-therapy with rifampicin (given with additional ritonavir). At 24 weeks 37/47 children (78.7%) in the >6 months age group and 26/33 (81.8%) aged <6 months had viral loads <50 copies/ml.

The investigators noted that the low age of initiation of treatment in this cohort reflected young infants with severe HIV disease rather than early initiation of treatment to prevent mortality and morbidity.

IMPROVED NEURODEVELOPMENTAL OUTCOMES

The developing brain is a major target for HIV. It is not yet known whether timing of initiation of antiretroviral therapy will affect neurodevelopmental outcomes in infants.

A substudy of CHER compared neurodevelopmental outcomes of 115 infants in this study from Tygerberg Children's Hospital with 84 control infants enrolled in a linked vaccine study, CIPRA-SA Project4.[9]

In this prospective study, the investigators looked at the neurodevelopmental profile, according to the Griffiths Mental Developmental Scales (GMDS), at 10 - 15 months of age in four groups of infants:

- HIV-unexposed, uninfected
- HIV-exposed, uninfected
- HIV-infected, HAART initiated before 12 weeks of age
- HIV infected, HAART deferred until eligibility criteria met.

The investigators were blinded to the infants' groups and a translator was used for Xhosa-speaking participants. Of 115 infants from CHER enrolled, 13 withdrew from the study and/or were not co-enrolled (10 early, 3 deferred), 8 died (all deferred) and 4 were excluded (3 early, 1 deferred).

The investigators found that infants initiated on early ART have significantly better locomotor and general scores on the GMDS at a median age of 11 months compared with infants on deferred HAART. Although mean quotients were lower on the other subscales in the deferred group, the differences were not significant. The mean scores on all subscales in the unexposed, uninfected group and the early HAART group were similar. They noted these results were 'despite careful monitoring and ready access to ART in the latter' (Table I).

TABLE I. MEAN QUOTIENTS OF INFANTS FOR DEFERRED V. EARLY HAART AND HIV-EXPOSED UNINFECTED AND UNEXPOSED INFANTS

	Deferred ART	Early ART	HIV-exposed uninfected	HIV-unexposed	*p*-value early v. deferred
No. assessed	26	66	28	34	
Median age in months (range)	11.0 (10.1 - 14.4)	11.0 (10.0 - 15.5)	11.4 (10.1 - 15.5)	11.5 (9.9 - 13.6)	
Mean locomotor quotient ± 1 SD	88.9±16.3	97.6±12.5	105.3±14.3	101.6±3.7	0.01
Mean general quotient ± 1 SD	100.1±13.8	106.3±10.6	106.0±10.1	106.9±11.7	0.02

TREATING CHILDREN EXPOSED TO SINGLE-DOSE NEVIRAPINE FOR PMTCT

Two studies looked at treatment of HIV-infected children with prior exposure to NVP to prevent MTCT.

Preliminary findings from IMPAACT 1060 confirmed concerns that NVP-exposed children could do less well receiving NVP containing HAART than protease inhibitor (PI)-containing HAART.[10,11]

This was a randomised trial of treatment-eligible children aged 6 months - 3 years conducted in seven African countries. NVP-exposed (cohort 1, *N*=288) and unexposed (cohort 2, *N*=288) children received either LPV/r or NVP plus 3TC and AZT. Children were stratified by age <12 months v. ≥12 months with an equal number to be enrolled in each age group.

A similar study of exposed and unexposed mothers had also been conducted (A5208). In this trial, the arm in which exposed mothers received NVP-containing HAART was stopped early by the Data Safety Monitoring Board (DSMB) owing to superior performance of the LPV/r-containing HAART arm.[12,13]

Following a scheduled DSMB review of IMPAACT 1060 on 20 April 2009, enrolment to cohort 1 also closed prematurely owing to a trend towards consistency with the A5208 results. At 24 weeks, virological failure (<400 copies/ml) was observed in 40% of the 60 infants <12 months v. 23% ≥12 months receiving NVP and LPV/r, respectively. Among the older children, 29% out of 22 and 17% of 19 receiving NVP and LPV/r experienced failure.

Several guidelines already recommend using LPV/r-based treatment for single-dose NVP-exposed infants. The NEVEREST study investigated whether NVP-exposed children, initially suppressed on LPV/r-based HAART, can safely switch to a NVP-based regimen.[14,15]

In this study children aged 6 weeks - 2 years and eligible for treatment (*N*=323) were initiated on LPV/r plus 3TC and d4T. Children achieving a viral load <400 copies/ml and stable for ≥3 months were randomised (*N*=195) to either remain on LPV/r (control, *N*=99) or switch to NVP (switch, *N*=96), and then followed up to 52 weeks.

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

They suggested that poorer adherence in the control group, due to the unpleasantness in taste of LPV/r syrup, may have led to more blipping and, in turn, unsustained viral suppression to 50 copies/ml during follow-up. In contrast, when they looked at sustained suppression to <1 000 copies/ml, 98% v. 80% of children in the control and switch groups achieved this (*p*=0.001). The investigators suggest that this study provides proof of concept that re-use of NVP is possible under some circumstances for HIV-infected children exposed to NVP prophylaxis and should be further investigated. They note that the clinical significance of low-level viraemia in the control group needs further study.

This group also showed data from an evaluation of lipid profiles in children in the control and switch groups.[16] They found no difference between the two groups at randomisation. But at 9 months after the change in regimen non-fasting total cholesterol (TC) and high-density lipoprotein (HDL) were significantly higher among the switch group (mean TC 4.13, HDL 1.36 mmol/l) compared with the control group (mean TC 3.73, HDL 1.07 mmol/l). Significantly lower triglyceride (TG) levels were found in the switch group (mean TG 1.36 mmol/l) compared with the control group (mean TG 1.53 mmol/l). They noted that the clinical significance of these non-fasting lipid changes requires further investigation.

Switching may provide a promising option for children originally initiated on PI-based HAART to preserve second-line options. At this stage, switching requires close virological monitoring after the switch in order to be done safely.

Another NEVEREST trial of efavirenz (EFV) v. LPV/r is planned in NVP-exposed children >3 years old.

These studies all underscore the limited treatment options available for children, particularly in resource-limited settings.

USING A NEVIRAPINE-CONTAINING FIXED-DOSE COMBINATION IN THE CHAPAS TRIAL

Paediatric fixed-dose combination (FDC) tablets provide simpler alternatives to liquids for children.

Cipla have produced scored, dispersible tablets of d4T/3TC/NVP (baby and junior Triomune) with the correct dose ratios for children.

A sub-study of the CHAPAS trial (Children with HIV in Africa Pharmacokinetics and Adherence of Simple Antiretroviral Regimens), in Zambia, evaluated the need for dose escalation of NVP.[17] This strategy is currently recommended but requires dosing with separate tablets, making initial treatment more complex.

Children were randomised to start antiretroviral therapy with full-dose nevirapine (Triomune a.m./p.m.) v. dose escalation, using an initial 14 days of half-dose NVP (Triomune a.m.; Lamivir-S (combined d4T/3TC) p.m.) followed by full dose. Children were dosed in accordance with WHO weight band tables. The primary endpoint was clinical/laboratory grade 3/4 adverse events (AEs) related to NVP.

In this comparison, 211 children aged 2 - 9 years with a median CD4 percentage of 13% were followed for a median of 92 weeks. Severe stunting, wasting and immunosuppression were common in the children. Seventeen children were lost to follow-up.

The investigators reported 31 (18 per 100 person-years) v. 29 (16.5 per 100 person-years) grade 3/4 AEs definitely/probably or uncertainly NVP-related in children receiving full-dose v. dose-escalation (incidence rate ratio (IRR) 1.09 (95% CI 0.63 - 1.87), p=0.74).

Twelve (11%) full-dose v. 2 (2%) dose escalation children had grade 2 disseminated skin rash and 1 receiving full dose had grade 1 rash. Two children (one from each arm) substituted with EFV; 3 continued full-dose NVP; 9 (8 full dose and 1 dose escalation) stopped NVP and restarted with successful dose escalation; and 1 full dose stopped, started a lower NVP dose, had another rash and substituted EFV.

Overall 90% of children who started with full-dose NVP continued uninterrupted in this study. As dose escalation requires provision of separate drug formulations, the evaluation of policy implications for dose escalation of NVP in fixed-dose combination HAART is ongoing.

The CHAPAS trial also investigated the pharmacokinetics of NVP in children treated with Triomune Baby/Junior and rifampicin-based TB treatment.[18]

EFV-based regimens are currently recommended for concomitant use with rifampicin, but EFV is not currently indicated for children below 3 years of age. Earlier CHAPAS data suggest that the higher dose ratio of NVP to NRTI in Triomune Baby/Junior may compensate for the dose reduction induced by rifampicin.

Pharmacokinetic sampling was performed in 22 children after 4 weeks of concurrent NVP and rifampicin-containing regimens. Rifampicin was dosed at 10 - 20 mg/kg per day. Samples were pre-dose (C_0) and 1, 2 and 6 hours post-dose, and NVP plasma concentrations were determined using LC-MS/MS. NVP pharmacokinetics in children without TB treatment (N=16) were compared in multivariate linear regression analysis. The median age of the 21 children analysed was 1.55 (range 0.66 - 3.18) years, and 10 were girls.

The investigators found that only 11 (52%) of the children receiving TB treatment reached sufficient NVP trough levels (C_0 <3.0 mg/l). Multivariate analysis revealed a 41% (95% CI 24 - 55%) reduction in NVP AUC with concomitant rifampicin. They noted a 3.4% increase in AUC for each 10 mg/m^2 increase in NVP dose/m^2.

They recommend caution with this approach in young children until more efficacy and safety data are available. They suggest that an increased NVP dose is likely to be necessary and requires further evaluation.

ONCE-A-DAY LAMIVUDINE AND ABACAVIR, AND ABACAVIR HYPERSENSITIVITY IN THE ARROW TRIAL

Simplification of HAART regimens provides benefit for children, caregivers and health workers. To date there are no data on once-daily use of 3TC and abacavir (ABC) in resource-limited settings.

A substudy from the ARROW trial (a randomised trial of monitoring and first-line induction-maintenance strategies) compared the PK of once- v. twice-daily 3TC and abacavir (ABC) (Kivexa).[19] This was a cross-over study performed in 41 Ugandan children aged 3 - 12 years receiving HAART, dosed according to weight bands. The ARROW trial uses scored tablets of ABC/3TC to ensure better accuracy of division and more flexible dosing. Total daily doses were 150+300 mg, 225+450 mg and 300+600 mg for children weighing 12 - 20 kg, 20 - 25 kg and >25 kg, respectively.

PK sampling was performed for twice-daily dosing at steady state (36 weeks) pre-dose, and 1, 2, 4, 6, 8 and 12 hours post dose. Children were then switched to the once-daily dose and further sampling was performed at 4 weeks with an additional sampling at 24 hours. Daily area under the curve (AUC_{0-24}) and peak level (C_{max}) were compared by geometric mean ratios (GMR). GMR with 90% CI within 0.80 - 1.25 was considered to be bioequivalent. PK parameters were available for 35 and 36 children for 3TC and ABC, respectively. Approximately half were in the younger age group.

The investigators reported that in children 3 - 12 years, AUC_{0-24} of both 3TC and ABC were bioequivalent with once and twice-daily regimens but C_{max} was 76% and 64% higher for 3TC and ABC respectively. No grade 3/4 adverse events were reported and no child discontinued after the switch to once-daily dosing.

In this analysis, in contrast to data from European children in PENTA 13, 3TC AUC levels in 3 - 6- and 7 - 12-year-old children were similar for both once- and twice-daily dosing and similar to levels in older children. The investigators noted that many younger children in PENTA 13, whose 3TC levels were lower, received syrups, but ARROW children received tablets. They concluded that these results suggest that once-daily dosing of 3TC and ABC is feasible in resource-limited settings.

The ARROW investigators also showed data describing successful management of hypersensitivity reactions among children in this trial in Uganda and Zimbabwe.[20]

The WHO recommends ABC for paediatric first-line treatment. Hypersensitivity reactions (HSR) occur in 2 - 5% of people receiving ABC in clinical trials and are strongly associated with the presence of the HLA-B*5701 allele. Prospective screening for HLA-B*5701 is sometimes recommended, but this pharmacogenetic test is rarely available in resource-limited settings.

Clinical diagnosis and management may be complicated in this setting due to widespread use of NVP and co-trimoxazole and febrile infections.
Health workers and caregivers were trained in recognition and management of ABC-HSR and all suspected HSR underwent independent clinical review. ABC was only discontinued in 7 cases.

The investigators reported that suspected ABC-HSR was rare (3/1 207, 0.2% (95% CI, 0.05 - 0.7%)) in this trial, consistent with reports of a lower prevalence of HLA-B*5701 in black populations. Clinical symptoms (fever, rash) occurred 9 - 13 days after initiation of HAART; 2/3 cases had additional gastro-intestinal and respiratory symptoms and required hospitalisation.

ABC-HSR was successfully managed despite co-administration of co-trimoxazole and NVP, and the investigators recommend that ABC can be used safely in resource-limited settings.

All references from 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 19 - 22 July 2009, Cape Town, unless otherwise stated.

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CPD QUESTIONS

Journal 36

Two CPD points are awarded for the correct completion and submission of the questions below.

CPD questionnaires must be completed online via www.cpdjournals.org.za.
After submission you can check the answers and print your certificate.
Questions may be answered up to 6 months after publication of each issue.
This programme is available free of charge to members of the HIV Clinicians Society and SAMA only.

1. True (A) or false (B) – click on the correct answer:
   The new SA HIV Clinicians Society Guidelines state that all infants under 2 years of age should start antiretroviral therapy (ART) irrespective of their CD4 count or clinical stage.

2. True (A) or false (B) – click on the correct answer:
   The Guidelines state that all infants under 1 year of age should start ART irrespective of their CD4 count or clinical stage.

3. True (A) or false (B) – click on the correct answer:
   The Guidelines state that tenofovir + FTC or 3TC is the ideal NRTI backbone for children.

4. True (A) or false (B) – click on the correct answer:
   The Guidelines state that abacavir + 3TC is the ideal NRTI backbone for children.

5. True (A) or false (B) – click on the correct answer:
   With regard to lipodystrophy, efavirenz has been implicated in lipomastia (fat deposited in the breasts).

6. True (A) or false (B) – click on the correct answer:
   Breast enlargement typically resolves without changing the regimen.

7. True (A) or false (B) – click on the correct answer:
   Lipo-atrophy of the face typically resolves without changing the regimen.

8. True (A) or false (B) – click on the correct answer:
   It is only necessary to substitute another agent for the offending agent when the lipo-atrophy is severe.

9. True (A) or false (B) – click on the correct answer:
   The commonest agent implicated in lipo-atrophy is stavudine (d4T).

10. True (A) or false (B) – click on the correct answer:
    With regard to changing ART in children, the regimen should be changed when the viral load returns to baseline.

11. True (A) or false (B) – click on the correct answer:
    An isolated viral load of 600 is called a blip and is a sign that the regimen must be changed.

12. True (A) or false (B) – click on the correct answer:
    Do not change therapy until adherence issues have been resolved.

13. True (A) or false (B) – click on the correct answer:
    3TC monotherapy should only be used as a temporary measure in a patient with a good CD4 level who has failed 3TC previously.

14. True (A) or false (B) – click on the correct answer:
    The M185E mutation is the classic 3TC resistance mutation.

15. True (A) or false (B) – click on the correct answer:
    With regard to the abacavir hypersensitivity reaction (HSR), HLA-B*5701 is common in black Africans.

16. True (A) or false (B) – click on the correct answer:
    Trimethoprim-sulfamethoxazole, nevirapine and efavirenz may cause a very similar HSR.

17. True (A) or false (B) – click on the correct answer:
    Only 50% of patients experience the HSR within 6 weeks after starting abacavir.

18. True (A) or false (B) – click on the correct answer:
    Fever is the most common manifestation of ABC HSR, occurring in 80% of cases.

19. True (A) or false (B) – click on the correct answer:
    Isolated gastro-intestinal symptoms such as nausea, vomiting, diarrhoea and abdominal pain may be a feature of ABC HSR, and ABC should be discontinued promptly if they occur.

20. With regard to immune reconstitution inflammatory syndrome (IRIS) in children, state which one of the following is TRUE:
    a) The most common cause of IRIS in infants in South Africa is tuberculosis.
    b) One of the differentials for paradoxical TB IRIS is resistant TB.
    c) BCG is never resistant to pyrazinamide (PZA).
    d) Kaposi's sarcoma does not present as an IRIS in children because it is a malignancy and not an infection.
    e) Steroids should be used in all cases of IRIS.