CONFERENCE REPORT

PAEDIATRIC OVERVIEW, IAS2009

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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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