CIPHER
Children Matter

Evidence for Action:

A Needs Assessment of HIV Research Priorities for Paediatric Populations

January 2013

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International AIDS Society
Stronger Together Against HIV

25 YEARS OF COMMITMENT

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Background

Why a needs assessment?

A recent update on access to evidence-based HIV interventions outlined the enormous progress made towards achieving universal access to antiretroviral therapy (ART) over the past decade while revealing significant gaps in the response to HIV, particularly in access to health sector HIV interventions for paediatric populations.[1]

The World Health Organization's (WHO) *Progress report 2011: Global HIV/AIDS response* revealed that HIV-infected children continue to suffer high morbidity and mortality rates in the first years of life. It also highlights the fact that infants and children have lower access to HIV diagnosis, treatment and care services compared with adult populations, and face a wide range of co-morbid conditions, including tuberculosis (TB), diarrhoeal disease, other microbial infections and malnutrition. While global access to the most effective antiretroviral (ARV) prophylaxis to prevent vertical transmission increased to 48% in 2010, early infant diagnosis coverage at two months was only 28%.[1] Important gaps remain in early identification of HIV-exposed infants, linkage to treatment programmes and retention in care between the third and fourth prongs of prevention of mother to child transmission (PMTCT) programmes.*

Globally, only 23% of children (15 years of age or younger) had access to antiretroviral therapy (ART) in low- and middle-income countries at the end of 2010 compared with 51% of adults. This underscores the need to improve clinical management and evaluate models of integrated care that will better serve the needs of paediatric populations. The rapid expansion of access to ART in low- and middle-income countries over the past decade has also resulted in a rapidly expanding population of HIV-infected and HIV-exposed uninfected (HEU) children and adolescents who are growing up and reaching sexual maturity. The need to develop evidence-based adherence support and sexual and reproductive health interventions tailored to these populations will be critical in the global AIDS response in the coming years.

The International AIDS Society (IAS) has worked to accelerate the research agenda for women and children through the work of its Industry Liaison Forum (IAS-ILF) and by identifying clinical and operational research questions aimed at improving access to more effective diagnostic, treatment and care interventions for paediatric populations. In March 2010, following a year-long comprehensive literature review and consultation process, the IAS released the consensus statement, *Asking the Right Questions: Advancing an HIV Research Agenda for Women and Children.* The recommendations in the consensus statement were endorsed by a wide range of global stakeholders working on paediatric research issues, including research funding agencies, civil society, advocacy organizations, industry and UN agencies.[2] Since then, the IAS has continued advocating for investments in these priority research areas, publishing research studies and commentaries through the *Journal of the International AIDS Society*, and hosting symposia, special sessions and satellites to help promote investment and implementation of the consensus statement recommendations.

Through an unrestricted grant from ViiV Healthcare's Paediatric Innovation Seed Fund, the IAS will expand its contribution to the paediatric HIV research field by launching the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER). CIPHER is a new flagship initiative of the IAS' Research Promotion Department. It is guided by a Scientific and Technical Advisory Committee (STAC) composed of clinicians, scientists and technical experts from around the world. CIPHER addresses two objectives: to invest in and promote priority paediatric research; and to strengthen paediatric cohort collaboration.

* PMTCT Prong three is HIV testing and counselling for all pregnant women and access to ARV prophylaxis for HIV-positive pregnant women before, during and after delivery; Prong four is better integration of HIV care, treatment and support for women found to be HIV positive and their families.

Objectives of this report

To ensure that CIPHER complements, rather than duplicates, opportunities for paediatric researchers available through other initiatives, research funding agencies or foundations, the first phase of the initiative was a comprehensive environmental scan and needs assessment, based on key informant interviews with technical experts on the STAC and an examination of peer-reviewed scientific literature published within the past two years.

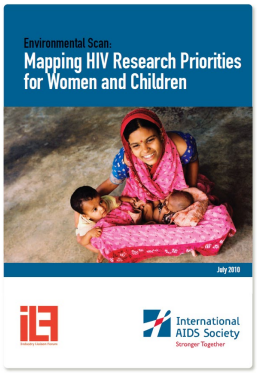
The current report, *Evidence for Action: A Needs Assessment of Paediatric HIV Research Priorities,* will inform CIPHER objectives and refine core activities within each objective. It is also intended that the needs assessment will support advocacy and collaboration among key stakeholders, including activities undertaken to strengthen paediatric cohort collaboration.

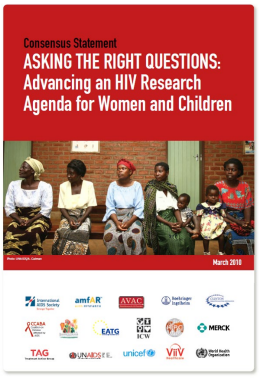
Methodology

The consensus statement, *Asking the Right Questions: Advancing an HIV Research Agenda for Women and Children,* released in January 2010, was based on a rigorous examination of peer-reviewed clinical and operational research literature and consultation with scientific, clinical and community experts (including a multi-stakeholder consultation in Cape Town, South Africa, in 2009).[2] *Mapping HIV Research Priorities for Women and Children* is an environmental scan that documents the results of the literature review and consultation.[2,3]

The current report builds on that evidence base and therefore includes only peer-reviewed scientific literature and abstracts published after the consensus statement was released. *Evidence for Action* includes abstracts from the 2nd, 3rd and 4th International Workshop on HIV Pediatrics, abstracts from the XVIII International AIDS Conference (AIDS 2010), abstracts from the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011), oral abstract presentations from the XIX International AIDS Conference (AIDS 2012) and relevant peer-reviewed scientific literature published from January 2010 to August 2012. Structured interviews were conducted with six technical experts from the CIPHER STAC.

The following pages reflect the key themes that emerged from key informant interviews, peer-reviewed literature and conference abstracts, and input from the CIPHER STAC. The literature review and key informant interviews suggest that the research priorities outlined in the 2010 consensus statement remain relevant to the paediatric research field. Key informants most frequently identified the following clinical and operational research areas, which were also prominent themes in the scientific literature.





Two of the key publications that informed this report. Above: Mapping HIV Research Priorities for Women and Children. Below: Asking the Right Questions: Advancing an HIV Research Agenda for Women and Children.

Clinical Research

Pharmacokinetic and Pharmacodynamic Studies

Clinical experts and available studies suggest that pharmacokinetic (PK) and pharmacodynamic (PD) studies of interactions between ARVs and drugs to treat co-morbidities, particularly tuberculosis, malaria and hepatitis, are critical for informing optimal clinical management of HIV-infected children.[4] Several recent studies have indicated the impact of such drugs as rifampicin on reducing therapeutic ARV drug levels, particularly with lopinavir (LPV).[5] Studies suggest that only when "super-boosting" LPV with increased doses of ritonavir is it able to reach clinically effective drug concentrations when co-administered with rifampicin, and such approaches may have significant hepatic toxicities and adherence challenges.[6, 7, 8]

Photo from UNAIDS / T. Znidarcic

PK and PD data on rifampicin and non-nucleoside reverse transcriptase inhibitors are more limited and variable, with some studies suggesting that rifampicin reduces drug levels of nevirapine, but not other ARVs in this class.[9,10] A small PK study among Thai children found that co-administration of rifampicin and a fixed-dose combination (FDC) of nevirapine (NVP), zidovudine (ZDV) and lamivudine at the higher end of the NVP dose range (200mg) resulted in therapeutically appropriate NVP exposure.[11] Given the high prevalence of TB and emergence of multi-drug resistant TB in sub-Saharan Africa and Asia, more PK and PD studies of ARVs co-administered with first- and second-line TB drugs are needed to inform clinical management of HIV/TB-co-infected children.

Approximately 85% of the 655,000 deaths due to malaria in 2010 were among children under five years of age, primarily in Africa.[12] The interaction of ARVs and malaria drugs among infants and children represents an important and understudied area of inquiry. Particularly given the backdrop of a developing immune system, evidence indicates that children co-infected with HIV and malaria are more likely to develop co-morbidities, such as anaemia or cerebral malaria.[4] Investigation of potential drug interactions between malaria drugs (particularly the five artemesinin-based therapies that the World Health Organization recommends for use as anti-malaria combination therapy) and paediatric ARVs are required to determine optimal timing and dosage in paediatric populations in malaria-endemic regions.

PK and PD studies are also required to inform optimal ARV formulations and dosage in the context of nutritional supplementation and rehabilitation interventions for malnourished infants and children.[4] PK and PD studies of paediatric ARV formulations and optimal therapeutic dosage with nutritional interventions would make important contributions to optimal clinical management.

HIV- and ARV-exposed uninfected infants are also subject to certain challenges. Studies have indicated that premature delivery and, in some studies, low birth weight are also a challenge for ARV- and HIV-exposed uninfected (HEU) children, particularly among those exposed to protease inhibitor-containing maternal regimens.[13]

Finally, presentations at the 4th International Workshop on HIV Pediatrics suggested that PK studies may also be important in providing information on adherence levels

given significant self-reporting bias in evaluating adherence, particularly among adolescents and older children.[14]

Optimal ART Initiation and Management

Updated 2010 World Health Organization (WHO) guidelines recommend ART initiation for all children two years of age and younger with an HIV diagnosis (based on virological testing if under 18 months, serological testing if over 18 months or presumptive clinical diagnosis). Available data suggest that the earlier ART is initiated (before significant attrition of CD4+ T cells occurs), the more effective it will be in reducing morbidity and mortality, accelerating neurocognitive and physical development and enabling CD4+ T cell recovery.[15] However, recent studies (including data from the PREDICT and PENTA 11 trials) suggest that the physical development (based on height-for-age and weight-for-age) and neurocognitive development of HIV-positive children lags behind their HIV-uninfected peers even when on ART.[16-19]

The PENTA 11/TICCH randomized controlled trial, which compared CD4+ T cell-guided treatment interruptions with continuous ART, found similar virological and immunological outcomes one and two years after the end of the trial.[20] Discussion and debate regarding this potentially controversial strategy at the 4th International Workshop on HIV Pediatrics was informed by data from the SPARTAC, CHER, PENTA 11/TICCH trials presented at the 2012 Conference on Retroviruses and Opportunistic Infections (CROI). It underscored the need for more definitive, longer-term studies in resource-limited settings to assess the relative risks and benefits of treatment interruption strategies in childhood and their impact on (among other measures) bone density, lipids, and metabolic, cardiovascular, hepatic and renal functions, as well as physical and cognitive development and the development of resistance.[21-23]

Optimal Paediatric ARV Formulations (First-line, Second-line and Salvage Therapy)

Clinicians remain challenged by the limited availability of optimal ARV paediatric formulations for first-line, second-line and salvage therapy. A cross-sectional analysis of the TREAT Asia and International Epidemiologic Databases to Evaluate AIDS (IeDEA) southern Africa regional cohorts indicated wide variability in access to paediatric formulations and in the regimens used (paediatric ART regimens were often not consistent with WHO normative guidelines).[24]

Recent results from the IMPAACT P1060 randomized controlled trial, which demonstrated the superiority of LPV/r-containing ART regimens compared with NVP-based regimens for HIV-infected infants regardless of exposure to sdNVP, may support updating normative guidelines. This will have implications for cost and accessibility of optimal paediatric ARVs in resource-limited settings.[25,26] The palatability (especially of LPV/r syrup) and limited availability of optimal paediatric ARVs remain significant challenges to closing the treatment access gap between adults and children. Evaluation of paediatric FDC formulations of drugs licensed for adults are required to establish a strong evidence base for updated normative guidelines for infants and children,[27] particularly given the possibility of drug resistance when maternal ART is unsuccessful in preventing vertical transmission. Additional studies of paediatric ARV formulations that take into account exposure to a growing range of maternal ART regimens are required to inform clinical practice and guidelines.

WHO released updated technical advice in June 2012, lowering the age of tenofovir (TDF)-containing paediatric regimens to children two years of age and older. TDF is associated with decreased bone mineral density in studies of both children and adults. Data in younger children in low- and middle-income countries (LMICs) is very limited.[28] Longer-term studies are needed to more definitively identify the impact of TDF-containing regimens on bone health and other biometric measures, especially in LMICs and in younger children where there is little data.

Evaluation of second-generation drugs, such as etravirine, and paediatric formulations from new drug classes, such as entry inhibitors and integrase inhibitors, will also be important for developing more options in the clinical management of infants and children.[29,30] Studies evaluating a range of drug delivery mechanisms of ARVs for infants and children, including sprinkles, powders, chewable tablets, nanotechnology and microparticles (such as the recent IMPAACT P1066 study of a raltegravir sprinkles and the CHAPAS 2 study of LPV/r sprinkles formulations), suggest that these innovations could provide important new treatment options for HIV-infected children that address long-standing palatability and adherence challenges of existing liquid and tablet formulations.[31-33]

Short-term and Long-term Impact of *in utero* ART Exposure on HIV-infected Infants, Children and Adolescents

WHO issued a programmatic update in April 2012 on ART for pregnant women and PMTCT to include "Option B+".[34] The programmatic update was driven by both the *Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping their Mothers Alive (2011-2015)* and additional evidence of the efficacy of ART in reducing the incidence of TB and other co-morbidities (even among individuals with high CD4+ counts).

Option B+ recommends lifelong triple-drug ART for all pregnant women regardless of CD4+ count. Many countries are now implementing Option B+ to help meet targets to end vertical transmission by 2015. Malawi's early implementation of Option B+ (in July 2011), with integrated clinical guidelines for PMTCT, ART and TB, resulted in significant uptake of maternal ART, both pre- and post-partum.[35] However, several clinical experts expressed concern that the impact of Option B or B+ on paediatric treatment outcomes is unclear, particularly given the expanded number of triple-drug options recommended for maternal ART, which now include TDF/emtracitibine- and efavirenz (EFV)-based regimens in addition to existing ZDV- and NVP-based regimens.

Questions also remain, for example, about the teratogenic effects of EFV when used during embryogenesis in the first trimester of pregnancy. A recent study indicates a higher rate of congenital anomalies in infants exposed to EFV in the first trimester compared with other ARVs, although a 2011 meta-analysis of 21 studies assessing teratogenicity among EFV-based (1,290 live births) and non-efavirenz-based regimens (8,122 live births) found no increased risk (RR 0.85).[36,37]

Renal dysfunction, changes in bone mineral density and reductions in body mass index (BMI) associated with TDF exposure has been a clinical concern for paediatric patients, with somewhat inconsistent findings on their clinical significance.[38,39] Data from a cohort of 25 children and adolescents, presented at the 4th International Workshop on HIV Pediatrics, found elevated levels of parathyroid

Photo from UNAIDS / Amnon Gutman

hormone (PTH) among children on TDF-containing ART regimens compared with those on TDF-sparing regimens, but it was unclear whether this would play a clinically relevant role in bone health and development.[40]

One of the points raised by several clinical experts is that much of the long-term health outcome data are from paediatric cohorts in high-income countries, and caution should be exercised in extrapolating results to populations in low- and middle-income countries given the much higher prevalence of malnutrition and other infectious diseases endemic in sub-Saharan Africa. A recent randomized controlled trial, consistent with earlier observational data, demonstrated that PI-containing maternal ART regimens result in a higher probability of premature delivery (but not increased hospitalization or mortality) compared with a triple nucleoside reverse transcriptase inhibitor regimen.[41] Recent data from a large observational cohort of HIV-infected children on ART in Kenya found low height-for-age and severe immune suppression associated with treatment-limiting ART toxicity.[42]

Both short-term neonatal outcomes (such as stillbirths, underweight and congenital anomalies) and long-term health outcome data are needed to assess ART-related toxicities and adverse events in resource-limited settings. Evidence on other potential long-term effects of ART exposure varies; impairment of myocardial growth (evaluated by measuring the thickness of the left ventricular wall) has been observed,[43] as have the metabolic dysfunction, reductions in bone mineral density and elevated cholesterol levels seen in adult populations.[4,44,45]

Worth noting is the need for simplified, standardized clinical tools for assessing developmental impairment among HIV-positive children on ART. The ASENZE study results of the Ten-Questionnaire screening tool, which assessed developmental disability in HIV-infected and HIV-uninfected children, suggests that simplified tools can help identify children at risk of developmental delays and impairment early, providing opportunities for interventions.[46]

Short-term and Long-term Impact of *in utero* ARV Exposure on HIV-uninfected Infants and Children

As maternal access to an increasingly diverse range of ART regimens expands, evaluating the short-term and long-term impact of exposure to maternal ARV *in utero* and during extended breastfeeding in infants and children is becoming increasingly critical.

A 2012 study of early growth parameters of HEU infants found no differences in birth weight for gestational age between those exposed to TDF-containing maternal ART regimens versus those without tenofovir, but slightly lower length-for-age and head circumference-for-age measures among TDF-exposed infants.[47] A sub-study of the South African Development of AntiRetroviral Therapy (DART) trial of HIV-uninfected infants exposed perinatally to TDF found no increase in congenital, renal or growth abnormalities after two years compared with (uninfected) population controls, with a similar mortality rate at one year of 5%.[48]

A PACTG cohort study of HEU children found normal motor and mental function scores of ARV-exposed children compared with ARV-unexposed children; a Botswana study found that lower birth weights in ART- and zidovudine-exposed uninfected infants were rapidly corrected during the first six months of life.[49,50] Other studies have indicated that ARV exposure *in utero* results in a higher prevalence of mitochondrial toxicity, haematological abnormalities and premature delivery (particularly in triple-drug maternal regimens).[13]

To date, studies of neurodevelopment of HEU infants with *in utero* exposure to ARVs have been reassuring, although data, in particular from resource-limited settings, is insufficient. Data presented at the 4th International Workshop on HIV Pediatrics suggested that although HEU children have delays in neurocognitive development compared with uninfected controls, the delays remain within standard deviations, with no differences in language and motor skills.[51] Longitudinal studies of HEU populations in resource-limited setting are required to more definitively assess long-term health and development outcomes of ARV-exposed uninfected children.

Optimal Approaches to Screening and Treating Co-morbidities and Malnutrition

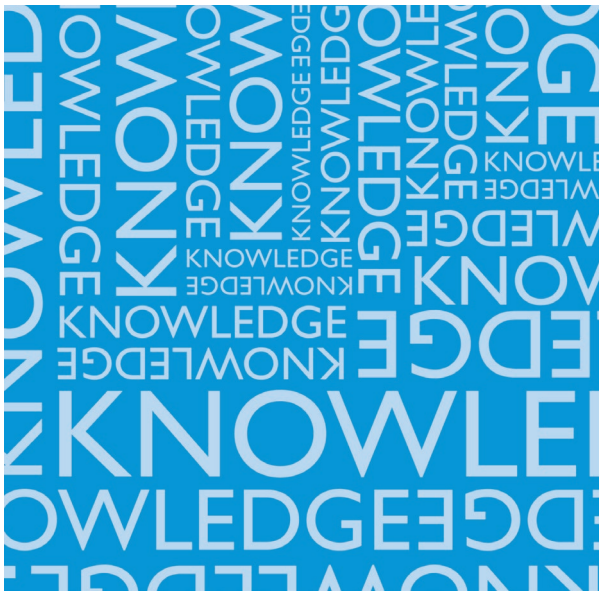
HIV-infected infants and children are at highest risk of mortality if they present later in disease progression with co-morbidities, such as microbial infections, oral candidiasis, TB and/or malnutrition.[52] Screening and treatment for active TB before ART initiation can reduce the incidence of active TB, but can be particularly challenging in paediatric populations.[53] Studies are required to determine optimal TB screening practices, isoniazid preventive therapy (IPT) and treatment for active TB among HIV-infected children.

Clinicians debated the relative merits, timing and conflicting scientific evidence of IPT pre-exposure prophylaxis for HIV-positive children at the 4th International Workshop on HIV Pediatrics; several recent studies have provided conflicting evidence of the best strategy for IPT administration in HIV-positive paediatric populations.[54-56] One consideration is the potential for resistance if IPT were broadly implemented.

Cryptococcal meningitis is a particularly challenging opportunistic infection (OI) for people living with HIV; recent estimates of the global burden of cryptococcal disease among people living with HIV (2007 data) revealed an incidence that is highest in sub-Saharan Africa at 3.2% (720,000 cases, 70% of which are fatal).[57] WHO recently released rapid advice on the prevention, diagnosis and treatment of cryptococcal disease among HIV-infected adults, adolescents and children.[58] Clinical experts noted the need for studies evaluating optimal approaches to screening and treatment of other OIs in paediatric populations (including optimal timing and co-administration of OI treatment with paediatric ARVs) to inform normative guidelines and clinical management.

Severe acute malnutrition is a major challenge for HIV-infected children in sub-Saharan Africa, resulting in a wide range of metabolic complications, such as electrolyte disorders, micronutrient deficiencies and infections.[59] A recent study of children initiating ART in a Kenyan clinic found that food and multivitamin supplementation was associated with increased monthly weight gains and height gains compared with population controls (younger age at ART initiation also strongly correlated with accelerated physical development).[60]

Observational data indicating a strong correlation between mortality and undernutrition among HIV-infected children on ART (particularly children under two years of age) in a Tanzanian cohort (including underweight, wasting and low weight-for-age indicators) underscore the need to evaluate optimal nutritional supplementation interventions.[61] Evaluating the most effective approaches to nutritional rehabilitation and supplementation is urgently required given the prevalence of malnutrition (and the attendant metabolic impairments) among HIV-infected infants and children in low- and middle-income countries. One of the challenges in determining the aetiology of underweight status among HIV-infected infants is the complex number of potential contributors, including TB and other OIs, as well as toxicities from ARVs and drugs to treat co-morbid conditions.



Operational Research

Interviewees noted that operational research studies are needed to address key programmatic issues for infants, children and adolescent populations. Several experts noted that operational research is an underfunded area that is key to identifying optimal settings and interventions for diagnosis, pre-ART care, clinical management (including adherence support interventions) and retention once children are enrolled in ART programmes.

Early Infant Diagnosis

Experts consistently identified access to reliable, sensitive and less expensive virological diagnostics for early infant diagnosis (EID) to be one of the most urgent needs for HIV-exposed infants in low- and middle-income countries. Studies have demonstrated the impact of delayed access to EID on increased mortality.[62] Evaluation of rapid-test protocols and less expensive virological assays (including dried blood spot assays to provide diagnostic results and baseline viral load) are required for EID in health care settings delivering maternal, newborn and child health services. Also, the prospect of new virological point-of-care assays may soon change the diagnostics landscape in resource-limited settings.

Results from the SAMBA trial, designed to evaluate a "test-and-treat" approach with the prototype SAMBA (Simple AMplification Based Assay) as point-of-care EID, delivered results with the reliability and sensitivity of traditional PCR assays.[63] Innovative approaches to improving earlier diagnosis have included offering it as part of childhood immunization clinics' activities.[64] A recent prospective study found that using a combination of physical indicators (including lymphadenopathy, oral thrush, dermatitis and weight) identified 86% of HIV-exposed and infected infants, and could help provide a presumptive HIV diagnosis for earlier referral to care.[65]

Linkage to and Retention in Care

WHO has emphasized the need for integrated, decentralized service delivery to expand access to HIV diagnosis and treatment interventions and reduce loss to follow-up.[66] Evaluating interventions and models of care aimed at improving linkages and referrals among HIV screening, pre-ART care and ART programme enrolment for children within PMTCT programmes and other health care settings was identified by several interviewees as key to improving paediatric health outcomes. A recent systematic review of PMTCT programmes in India, for example, found significant attrition at each stage of the cascade, particularly before pregnant women received ART.[67] Loss to follow-up varies widely across regions; a recent multi-regional analysis identified contributing factors as recent ART initiation, increased cohort size, fee for services and overburdened health facilities.[68]

Photo from UNAIDS / C. Giray

Malawi's experience in moving to an "Option B+" approach in July 2011 included accelerating the decentralization of health care to the lowest level of the health care system and integrating clinical guidelines on HIV services (including PMTCT, pre-ART, ART and early infant diagnosis and testing): the number of pregnant or breastfeeding women

starting ART rose from 18,000 at the end of June to 34,000 at the end of December.[69] The integrated approach taken by Malawi also incorporates EID, family planning and under-five clinical guidelines. The monitoring and evaluation framework, which was implemented in conjunction with Malawi's move to an "Option B+" approach, should provide important national data regarding the impact of this approach on infant diagnoses and ART access for infants. Evaluating the most cost-effective models of integrated care (e.g., ART management with immunization, family planning and school-based health programmes) are key to improving retention in the cascade of care.

Adolescent Adherence and Transition from Paediatric to Adult ART Programmes

A key question raised by several experts regarding research priorities is how best to manage the rapidly growing number of HIV-positive adolescents in ART programmes, including evaluating optimal approaches to delivering sexual and reproductive health services and age-appropriate adherence support. Studies have indicated that both adherence and virological response (including shorter time to viral rebound among those who achieve viral suppression) is poorer in adolescent populations than in adult or pre-adolescent populations.[70,71] Little data are available on evaluating interventions and models of care that are most effective in supporting adherence among adolescents, and in transitioning adolescents from paediatric to adult ART programmes.

Disclosure, Psychosocial Support and HIV/STI Prevention

Evaluations of psychosocial and HIV prevention interventions for adolescents were identified as important research areas, particularly among street-involved and/or at-risk youth. Recent data from a US cohort of perinatally HIV-infected youth indicated that more than half of those who were sexually active were having unprotected sex.[72] A multi-centre study of five paediatric clinics in Mali, Senegal and Côte d'Ivoire found that two-thirds of the 650 children over 10 years of age on ART were unaware of their HIV status.[73] Follow-up data at 36 months indicated a strong correlation between HIV disclosure and retention in care (93.1% of those who were aware of their HIV status were retained in care versus 62.2% of those who were unaware of their HIV status).

A large, multinational cross-sectional study (Malawi, Mozambique, Zimbabwe and Zambia) found that some of the key challenges facing adolescents living with HIV were disclosure, accessing information on sexual and reproductive health (including family planning), and supportive family and health care environments.[74] Data from the Baylor Pediatric AIDS Initiative in Botswana found that two-thirds of school-age children missed school at least once in the preceding month due to HIV and 31% indicated that their illness affected their school performance.[75]

Identifying effective, family-based approaches for parents to inform their HIV-positive children about their serostatus and interventions to support HIV and sexually transmitted infection (STI) prevention and family planning services among adolescents prior to sexual debut are also important issues for which there is limited evidence in the scientific literature. Recent studies in both high-income and resource-limited settings found a high rate of unplanned pregnancies (more than 80% of an HIV-positive adolescent cohort in the UK and Ireland reported one or more unplanned pregnancies) and relatively low rates of condom usage as a result of multiple contributing factors, including self-agency in negotiating safer sex, peer pressure regarding sexual activities and pregnancy, drug or alcohol use, and transactional and trans-generational sex.[76-78]

Studies have also underscored the disproportionate impact of HIV risk among adolescent sub-populations, such as young girls who, as a result of both social and biological factors, are more vulnerable to HIV infection. Similarly, gay, lesbian and bisexual youth face unique challenges, as demonstrated by a recent South African study. Discussion at the 4th International Workshop on HIV Pediatrics highlighted the need to establish long-term studies on the efficacy and sustainability of behavioural interventions targeting this population. Clinical experts also noted that how best to deliver emerging ARV-based biomedical prevention interventions (such as Truvada™, which in July 2012 was the first-ever drug licensed to prevent HIV infection), as well as studies of ARV-based gels and vaginal ring microbicides, will become increasingly important with a growing number of serodiscordant adolescent couples, although clinical data evaluating such interventions among adolescent populations are currently lacking.

Critical Research Gaps

Key informants stressed that CIPHER represents an opportunity to conduct retrospective and prospective studies and analyses of data from existing paediatric cohorts (including opportunities to pool and analyze data across cohorts) in both high-income and low- and middle-income countries to answer some of these questions. Interviewees strongly supported the idea of CIPHER as a "knowledge broker" that is able to bring together experts to analyze data from disparate cohorts.

The following clinical and operational priority research focus areas were identified through the study of peer-reviewed scientific literature, which were mentioned in the previous sections; they were verified in key informant interviews with technical experts and in consultation with the STAC. These priorities represent research questions that are urgently required to develop optimal interventions and approaches to HIV clinical management and service delivery, and underscore the unique needs of paediatric populations.

Clinical Research Priorities

- Pharmacokinetic and pharmacodynamic studies of paediatric antiretrovirals and drugs for co-morbid conditions (particularly for TB, malaria, other common childhood illnesses and nutritional interventions for malnutrition).
- Studies evaluating optimal antiretroviral therapy initiation, long-term management and complications in children (especially children over two years of age) and adolescents.
- Studies evaluating the short-term and long-term impact of *in utero* exposure to maternal antiretroviral therapy and the short-term and long-term impact of paediatric antiretroviral therapy on physical and cognitive development of HIV-infected infants, children and adolescents (key areas include neonatal outcomes, metabolism, bone mineral density, and other clinically-relevant laboratory and biological markers).
- Studies evaluating the short-term and long-term impact of *in utero* exposure to maternal antiretroviral therapy on physical and cognitive development of HIV-exposed uninfected children and adolescents.
- Studies evaluating and/or validating diagnostic assays to assess neurocognitive and physical development among HIV-infected and HIV-exposed uninfected infants and children in resource-limited settings.
- Evaluations of the most effective interventions to treat HIV co-infections and co-morbidities among children including TB, malaria, other common opportunistic infections and malnutrition.

Operational Research Priorities

- Evaluations of interventions to improve access to reliable early infant diagnostics, including rapid test protocols.
- Evaluations and/or validation of simplified, standardized diagnostic tools to assess neurocognitive and physical development in HIV-exposed infected or uninfected infants, children and adolescents in resource-limited settings.

- Studies evaluating interventions and optimal models for integrating paediatric HIV services with maternal, newborn and child health and other health services.
- Studies evaluating interventions and optimal models for promoting early post-natal and long-term programme retention and reducing loss to follow-up.
- Studies evaluating optimal approaches to support childhood and adolescent adherence and transition to adult antiretroviral therapy programmes.
- Studies evaluating the most effective interventions to support disclosure, access to psychosocial and sexual and reproductive health services, delivery of biomedical HIV and STI prevention interventions for adolescents.

Conclusion

The research priorities outlined in the 2010 consensus statement, *Asking the Right Questions: Advancing an HIV Research Agenda for Women and Children*, remain relevant to the paediatric research field. A major barrier to developing optimal interventions and approaches to HIV clinical management and service delivery for paediatric populations is that in many areas there is either limited or no data on infants, children and adolescents, especially in low- and middle-income countries. The role of CIPHER as a forum for strengthening cohort collaboration is supported by key informants. The main areas of clinical and operational research and the identified research priorities outlined in this document will serve as a basis for guiding future CIPHER activities.

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25 YEARS OF COMMITMENT