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Introduction

HIV/AIDS was in 2006 the leading cause of death worldwide for people aged 15 to 49 years. The pandemic is having a dramatic impact on child mortality, with 380,000 children who died of AIDS-related diseases [1]. The same year, it was estimated that 2.3 million children under the age of 15 years were living with the virus, mainly as a result of mother-to-child transmission of HIV (MTCT) [1]. More than 90% of these children were living in sub-Saharan Africa. The number of children orphaned after their parent(s) died from AIDS is also rising dramatically, reaching 15.2 million children worldwide in 2005. More than five million children are currently living with HIV-related chronically ill family members and will become orphans unless appropriate care and treatment is provided [2].

Considerable progress has been achieved in industrialised countries towards the prevention of new paediatric HIV infections, the provision of adequate treatment to HIV-infected children, and the support to vulnerable children and orphans affected by HIV/AIDS. But for many children, especially in low-incomes countries (LINCs), adequate prevention, care and treatment still remains inaccessible.

The aim of this article is to review the state of knowledge in the field of paediatric HIV/AIDS, to describe the research undertaken over the past decade, and to assess the level of implementation of research results, focusing mainly on the experience of African countries.

The prevention of mother-to-child transmission of HIV (PMTCT)

Most paediatric HIV infections are the result of MTCT, which can occur in peri-partum, during late pregnancy and delivery, and post-partum, through breastfeeding. In the absence of any intervention, the risk of MTCT is 15-30% in non-breastfeeding populations

and 20-45% among populations who practice prolonged breastfeeding, which is of particular concern in Africa [3]. In developed countries, the risk of MTCT can be reduced to 2% through the combination of several preventive interventions: antiretroviral (ARV) prophylaxis administered to women during pregnancy and labour and to infants during the first weeks of life, elective caesarean delivery, and complete avoidance of breastfeeding [4]. In LINCs however, caesarean delivery is seldom feasible [5] and it is often neither acceptable nor safe for mothers to refrain from breastfeeding in the absence of any specific nutritional support. In these settings, efforts to prevent HIV transmission in infants were thus initially focused on peri-partum MTCT.

Since 1998, the efficacy of short-course peri-partum ARV regimens administered to HIV-infected pregnant mothers and their newborn, has been established within African and Thai randomized clinical trials [6-9]. These regimens, involving three ARV drugs – zidovudine (ZDV), lamivudine (3TC) and nevirapine (NVP) – resulted in MTCT risk reductions ranging from 37% to 77% compared to no intervention. Combination regimens are more efficacious than single-drug regimens [10-12], as are regimens of longer durations compared to short-course and single-dose regimens [13]. The World Health Organisation (WHO) currently recommends the following ARV regimen for preventing MTCT among women who do not have indications of ARV treatment (ART) for their own health: ZDV from 28 weeks of pregnancy; ZDV and 3TC + single-dose (sd) NVP at the onset of labour; maternal ZDV + 3TC for seven days after delivery; and sd-NVP + one week of ZDV for newborns [4]. Within LINCs who are able to deliver only a minimal range of ARVs, the sd-NVP regimen remains the most feasible and least expensive strategy, with residual peri-partum transmission rate of 12% [7, 14]. Although the selection of NVP-resistant virus after the administration of a sd-NVP is frequent [15, 16], this biological event can be reduced by the addition to sd-NVP of a short three-day postpartum combination of maternal ZDV+3TC

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[17, 18]. It is now clearly acknowledged that pregnant women in need of ART should initiate treatment as soon as possible [4]. ART improve the woman's health and is also expected to reduce the maternal HIV plasma viral load, the strongest determinant of MTCT [19, 20]. Although ART initiated before or during pregnancy may be associated with adverse pregnancy outcomes, in particular with prematurity [21, 22], to date, the benefits of ARV exposure greatly outweigh any observed risk for the mother or infant [23].

Research has also addressed the long-term efficacy of peri-partum interventions, e.g. after complete cessation of breastfeeding. A diminution or even a loss of efficacy of short-course ARV regimens administrated in peri-partum in African breastfeeding populations was reported [24]. Postnatal interventions aimed at the prevention of HIV through breastfeeding are thus critical to achieve an overall substantial and sustainable reduction in MTCT. Breastfeeding is the most nutritionally-adequate infant feeding practice, also providing protection against diarrhoea and acute respiratory infections, especially in early life [25]. Yet, in the absence of any targeted postnatal intervention, breastfeeding is also responsible for 8.9 HIV infections per 100 child-years of breastfeeding and accounts for 40% of paediatric HIV infections [3] [26]. Furthermore, the longer the breastfeeding duration, the higher the resulting risk of postnatal transmission of HIV [24, 27, 28]. Breastfeeding beyond six months is a strong determinants of HIV transmission [28]. The assessment and implementation of interventions to prevent postnatal HIV transmission that will balance this risk of MTCT with the possible adverse outcomes for mother and child health is therefore a challenge.

The first alternative to prolonged breastfeeding is the complete avoidance of breastfeeding, substituted by infant formula. This strategy is currently enforced in Europe and the United States, but the situation is more complex in LINCs. A second alternative is to shorten the duration of breastfeeding, with an early cessation implemented around six months of age. A third potential intervention consists in the promotion of exclusive breastfeeding, e.g.

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without introducing any other fluids or solids than breastmilk during the first months of life [29-31]. The combination of these last two interventions reduces the cumulative risk of HIV postnatal transmission while retaining the benefits of exclusive breastfeeding during the first months of life.

Given the necessary support, the acceptability of formula feeding and early breastfeeding cessation was high in Abidjan, Côte d'Ivoire [32, 33]. In this research setting, no excess in mortality at 18 months was observed in children exposed to alternatives to prolonged breastfeeding when taking into account HIV status [34]. Similarly, in Botswana, the time-to-mortality distributions through 18 months of age were not significantly different between infants receiving six months of breastfeeding plus prophylactic infant ZDV or formula feeding plus one month of ZDV [35]. However replacement feeding was associated with higher mortality, morbidity, and stigma in less supported field settings [36, 37]. Preliminary results from studies conducted in Zambia, Malawi and Kenya suggest increased rates of diarrhoea among children breastfed for six months [38-40]. HIV-infected pregnant women must be counselled in choosing a feeding practice adapted to their individual situation, and be supported in their feeding choice after delivery [41, 42].

Other postnatal interventions for PMTCT include the inactivation of the virus in breastmilk via heat treatment, but their use in a domestic situation requires further practical developments [43, 44]. Finally, studies have recently explored the benefits of ARV regimens designed to provide maternal treatment, reducing the maternal plasma HIV viral load, and/or post-exposure prophylaxis to infants during breastfeeding, and thus reduce the risk of MTCT in settings where breastfeeding is common [35, 45]. Research is currently underway to assess the interest of these strategies [46].

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Overall, research has demonstrated that the combination of peri-partum and postnatal interventions considerably reduces MTCT rates with a long-term benefit sustained until age 18-month [47]. HIV counselling and testing, ARV prophylactic regimens and infant feeding interventions constitute the basic package of PMTCT services. The proportion of pregnant women being offered PMTCT services has slightly increased from 7.6% in 2003 to 9% in 2005 in LINCs [48], but the global PMTCT coverage remains unacceptably low worldwide. In 30 African countries with the highest HIV prevalence, only 5% of HIV-infected women currently access PMTCT interventions [48]. Operational research initiatives have explored some of the barriers to PMTCT [49-51]. The implementation of PMTCT services is strongly hindered by the quality of operating health systems [52, 53], especially in rural areas: lack of decentralised services, poor monitoring, frequent stock ruptures of test kits and ARVs. The promotion of an "opt-out" approach to prenatal HIV testing [54, 55] and, more generally, the adoption of the recently recommended WHO strategy for provider-initiated HIV testing [56] are likely to improve PMTCT coverage. The lack of involvement of male partners is also underlined; pregnant women who are unable to share their HIV status with their partner may be reluctant to accept interventions that would identify them as being HIV-infected [57, 58]. Finally, innovative family approaches linking the access to HIV care with HIV prevention efforts are a critical step towards improving the transition from PMTCT research to wide-scale practice, but need to be rolled out [19].

Paediatric HIV/AIDS care

In LINCs, it is estimated that 50% of HIV-infected infants will die before the age of two [59]. Early paediatric HIV diagnosis is thus critical to allow the timely start of appropriate treatment, reduce morbidity and mortality, guide decisions related to child

nutrition and improve the quality of life of HIV-infected children [60]. In many LINCs however, access to early paediatric HIV diagnosis depends on the local laboratory capacity and the availability of tests, and is often considered too costly and complex. To date, real time Polymerase Chain Reaction (PCR) is the most valuable and least expensive (<20 euros) technology to detect HIV-RNA among infants under 18 months of age [61]. Although this technology requires good laboratory infrastructure and human skills, its routine use for programmatic purposes should be encouraged [4]. In rural areas, a dried blood spot (DBS) is used for collection and storage of blood samples [62, 63], although DBS samples still need to be referred to a central laboratory for HIV testing [64]. It is expected that DBS will become the standard tool for improving the coverage of early paediatric HIV diagnosis in LINCs.

Following the confirmed diagnosis of HIV infection, the baseline clinical and laboratory assessment for children should include the clinical staging of HIV disease and measurement of CD4 and T-lymphocyte [63].

The prevention of opportunistic infections (OI) such as tuberculosis or Pneumocystis Pneumonia [65] has been the standard of paediatric HIV care for many years. In South Africa, isoniazid prophylaxis reduced the incidence of tuberculosis in HIV-infected children and improved their survival [66]. A Zambian trial demonstrated the efficacy of cotrimoxazole prophylaxis in children older than 12 months [67]. All HIV-exposed children should thus receive cotrimoxazole prophylaxis from age 6-week in resource-limited settings, irrespective of locally-identified resistance to this drug, as recently recommended by WHO [68]. Yet, although cotrimoxazole costs as little as US$ 0.03 a day, UNAIDS estimates that 4 million children who need this drug do not access it [48].

ART helps HIV-infected children to preserve, enhance, and reconstitute their immune system and therefore reduce the risk of OIs; to suppress HIV replication; to restore their growth; to improve mental functioning; and overall their quality of life [69-72]. The decision-

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making process for initiation of ART in children in LINCs relies on clinical and/or immunological assessment [63]. Despite nearly 15 years of experience in the treatment of HIV-infected children in Europe and in the USA [73], considerable uncertainty remains as to when to start ART. Indeed, the benefits of early ART initiation [74, 75] need to be balanced against the costs and drawbacks of ART (quality of life, lifelong therapy, viral resistance, adverse effects, and limited second and third-line regimens). The WHO recommends that all children classified as WHO paediatric clinical stage 3 or 4 can start ART regardless of CD4, TLC or availability of virologic test results. Recent data from South Africa from the CHER randomised trial showed that starting antiretrovirals within the first 12 weeks of life, rather than starting at the current WHO recommended CD4 threshold of 20%, lowered the risk of death [76].

However, only a handful of ARVs in the current WHO guidelines have solid formulations in doses appropriate for paediatric use and paediatric fixed-dose drug combinations are scarce. Although three recent studies showed satisfactory virological and immunological benefits in children receiving an adult's fixed-dose combination antiretroviral therapy in fractions [77-79], the lack of pharmacokinetic and pharmaco-dynamic data on the ARVs available to children still contributes to HIV-infected children being under-dosed in ARVs [80]. There is an urgent need for additional drug formulations for children [81]. In 2007, the first line ARV regimen recommended by WHO for children includes NVP. However, the immunological and virologic response in infants exposed to NVP remains of much concern [82] and should be further documented.

Additional research is also critically needed regarding the support to families and health workers who disclose HIV infection to the child [83], and the psychological development of children. A recent South African study reported a 26% disclosure rate among children aged under six years [84], although the importance of paediatric disclosure was

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unanimously acknowledged. The absence of HIV disclosure to a child is associated with non-adherence to treatment [85-87].

Safe and adequate paediatric HIV/AIDS care deserves further research. The implementation and management of a comprehensive package of services for the care of HIV-infected children requires a minimum quality of health services, in terms of human resources and technical equipment, and is thus a major challenge for all-level health facilities in LINCs.

The provision of paediatric HIV/AIDS care at district level

The expected wide-scale introduction of ART for children is indeed only one aspect of a successful care, support and treatment approach. A comprehensive continuum of care for children should also include HIV counselling and testing, cotrimoxazole prophylaxis for both HIV-exposed and HIV-infected children, regular follow-up of HIV-infected children, and community-based support and counselling of caregivers.

However, in many LINCs, such comprehensive paediatric HIV/AIDS care faces numerous challenges within the local district health system [88]. The lack of health staff and inadequate health-care infrastructure is one of the first constraints to the scaling–up of HIV/AIDS care services. Health professionals required to care for HIV-infected children are in short supply in Africa [89]. The identification and referral of children in need of HIV/AIDS care (coming from inpatient ward, adult ARV programmes, rural clinics, community-based organisations, or PMTCT programmes) is also poor. In South Africa, only 10% of children requiring HIV testing at 12 months were actually tested [90]. The improvement in local patient monitoring [91], the decentralization and extension of PMTCT and HIV/AIDS care and support infrastructure into poorly serviced areas, combined with the deployment of mid-level professional cadres and community level heath workers [92, 93] are examples of

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possible solutions. Anonymous HIV screening of all infants at immunization clinics is also feasible to identify HIV-infected children early for referral into care and treatment programmes [94].

Evidence-based guidelines on paediatric HIV/AIDS care, adapted to the capacity of each health facility, are essential. The specific assessment and management of symptomatic HIV infection at primary health care level was recently integrated within the WHO Integrated Management of Childhood Illness (IMCI) guidelines, and evaluated in South Africa [95]. Additional prospective assessments of clinical algorithms is still required to improve paediatric care and treatment [96]. Experience in adult care [97-99] and recently in African children [100, 101] advocates for free access at the point of service delivery to paediatric HIV care and treatment including ART.

The various operational constraints to paediatric HIV/AIDS partly explain why currently children represent only 6% of the overall population receiving ART, when this age group represents 14% (n=600,000) of the total population in need of ART [48]. However, political leadership in the fight against HIV/AIDS is steadily growing and several ART programmes are now accessible to children in resource-poor settings [69, 71, 72, 79, 102-109].

The research and programmatic experience of caring for children living with HIV-infected family members is also very scarce and highlights the many gaps remaining in the economical, political and social response to children affected by HIV/AIDS.

Children affected by HIV/AIDS

In LINCs, the vulnerability of children affected by HIV/AIDS is first physical, and mainly related to the impact of HIV/AIDS on household economies. The illness or death of a

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breadwinner leads to difficulties in responding to the basic needs of family members, including accessing ARV drugs. Thus, uninfected children born to HIV-positive mothers experience their mother's illness and death at a young age, which contributes to putting them at risk of increased morbidity and mortality [59, 110, 111]. To date however, there is only limited evidence of ill health among young orphans who have survived their mother's death [112, 113].

The psychological impact of HIV/AIDS on children in LINCs has been greatly underestimated. And yet, the world of a child living in a family affected by HIV/AIDS goes through many changes. These children have to witness the physical deterioration and pain of their HIV-infected parents, especially when they are unaware of the nature of the illness affecting their parent(s) or refuse to acknowledge HIV infection. Children are anxious about their source of livelihood and their ability to retain the family home after the parent's death; separation from siblings is a frequent and important source of trauma [114, 115]. The serial loss of adult figures and carers such as parents, teachers or mentors is also likely to create a sense of insecurity or abandonment. Overall, much remains to be understood on the psychological consequences of HIV/AIDS among children, including the specific emotional effects by age, type of orphan and living arrangements.

Research and interventions studies on counselling, emotional and social support for children affected by HIV/AIDS are scarce and mostly focused on the specific difficulties and traumas of orphans. In rural Uganda, access to mental health services was shown to benefit to all orphans, regardless of family situations [116]. However the number of health workers specializing in mental health remains insufficient in most LINCs [117]. In Zimbabwe, peer education programmes involving the community and developing ties between orphans and non-orphans, have build up the self-esteem of children affected by HIV/AIDS and discouraged stigmatisation [118]. Schools also play a significant role in the socio-emotional

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development of children, especially of orphans and children affected by AIDS. Unfortunately, in countries severely affected by the HIV/AIDS epidemic, the supply and quality of education services are severely constrained [119]. In Zimbabwe, orphans were less likely to be enrolled in school than non-orphans of the same age, due to poverty, to the priority given to core family children and to stigmatisation [120].

The legislative and governmental support to children affected by HIV/AIDS is influenced by the stability of the political environment, which is rare in many of the countries severely hit by the HIV/AIDS epidemic [121]. In 2003, of the 40 sub-Saharan countries with generalized epidemics (adult HIV prevalence reaching 1% or above), only six (15%) had developed a national policy on orphans and HIV/AIDS. [122].

This breakdown in governmental support systems may explain why families and communities have been described as the key caregivers of children affected by HIV/AIDS. In traditional African cultures, the practices of child fostering, by which children are cared for by non-biological parents, predate the HIV epidemic [123, 124]. In the era of HIV, these traditional practices have been preserved [125][126]. Still, there is concern on whether child fostering within the extended family will be able meet the expected increase in the number of orphans [127, 128]. This concern has encouraged the development of community-based initiatives from “external actors” (other than families) to endorse orphan care: residential community centres [129]; small, family-based orphanages; or orphanages supported by donors sponsoring NGOs [130]. Many of these orphan care strategies have been shown to be inadequate for large-scale implementation and unsustainable because based on donor funding. Overall, research has shown that caregivers of children affected by HIV/AIDS and service providers tend to work in isolation from each other, with little networking between approaches [121].

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A number of model frameworks have been developed by Family Health International [131] or USAID [132] for responding to the needs of children affected by HIV/AIDS and orphans. By the end of 2005, nearly 30 diverse organisations had endorsed the USAID framework, signalling wide acceptance to shape effective responses to the growing problem of children affected by HIV/AIDS [48].

Conclusion

During the past two decades, international efforts to fight against HIV/AIDS have yielded important research successes for child survival in LINCs. However the transition from research to action remains largely insufficient. Improving the coverage of PMTCT should be a priority. There is also enough evidence today to roll out paediatric HIV care and treatment, at least at the same speed and extent than adult care. This however requires improving health care systems as well as political commitment and funding at international and national levels. Current knowledge indicates that orphans and vulnerable children pay a large tribute to HIV/AIDS and deserve a large-scale response. Finally, the fight against HIV/AIDS requires the scaling-up and intensification of primary HIV prevention, as part of a comprehensive response that simultaneously expands access to treatment and care.

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