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Review

Challenges and perspectives of compliance with pediatric antiretroviral therapy in Sub-Saharan Africa

Défis et perspectives de l'observance du traitement antirétroviral pédiatrique en Afrique subsaharienne

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Abstract

More than 3 million children aged less than 15 years are infected with HIV worldwide, mainly in Sub-Saharan Africa. The survival of HIV-infected children depends on their access to antiretroviral therapy whose success mainly depends on a good life-long compliance with antiretroviral therapy. Given its complexity and specificity, assessment and monitoring of pediatric compliance with antiretroviral therapy is a major challenge. There is no consensus on a gold standard for monitoring compliance with antiretroviral therapy. Compliance is also influenced by many factors related to the child, the caregiver, the healthcare staff, the healthcare system, and antiretroviral drugs. This review aimed to assess scientific knowledge on pediatric compliance with antiretroviral therapy in Sub-Saharan Africa, and to identify areas for future interventions to improve compliance. Good compliance is essential to achieve the “90% coverage of children on antiretroviral therapy” gold standard of the World Health Organization, and to eliminate HIV infection by 2030.

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Keywords: Compliance; Africa; HIV; Pediatric antiretroviral therapy

Résumé

Plus de 3 millions d'enfants âgés de moins de 15 ans vivent avec le virus de l'immunodéficience humaine (VIH) dans le monde, dont la majorité en Afrique subsaharienne. La survie de ces enfants infectés par le VIH est conditionnée par leur accès à un traitement antirétroviral, dont le succès dépend essentiellement d'une bonne observance maintenue au long cours. L'évaluation de l'observance du traitement antirétroviral pédiatrique représente cependant un défi important compte tenu de sa complexité et de sa spécificité. Plusieurs méthodes de mesure de l'observance ont été développées mais aucune de ces méthodes ne présente toutes les qualités indispensables pour devenir la méthode de référence. L'observance du traitement antirétroviral est également influencée par de multiples facteurs liés à l'enfant, à la personne en charge de ses soins, au personnel de santé, aux systèmes de santé et aux médicaments antirétroviraux. Cette revue générale de la littérature a pour objectif de faire l'état des lieux des connaissances sur l'observance du traitement antirétroviral pédiatrique, en particulier en Afrique subsaharienne, et d'identifier des pistes d'interventions futures pour l'amélioration de l'observance afin d'atteindre 90 % de suppression virologique chez les enfants traités par antirétroviraux conformément aux objectifs de l'ONUSIDA qui visent l'élimination de l'infection à VIH d'ici 2030.

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Mots clés : Afrique ; Observance thérapeutique ; Traitement antirétroviral pédiatrique ; VIH

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1. Introduction

Despite significant progress made in preventing mother-to-child transmission of the human immunodeficiency virus (HIV), the HIV pediatric epidemic continues to grow worldwide. HIV-infected children aged below 15 years were estimated at 3 million in 2013; more than 90% of them lived in Sub-Saharan Africa [1]. The number of new infections among children was estimated at 240,000 [210,000–280,000] in 2013 [2]. Disease progression is faster in children than adults. In the absence of intervention, the mortality rate of these infected children is extremely high and early mortality is observed, reaching 50% at the age of 2 [3].

The use of highly active combinations of antiretroviral drugs led to a sharp decrease in the mortality and morbidity rates of HIV-infected people [4]. Antiretroviral drugs are increasingly available and several studies demonstrated the efficacy of pediatric antiretrovirals in Africa and worldwide [5,6]. HIV infection used to be considered a fatal disease; it is now a chronic infection that requires a life-long treatment. However, access to antiretroviral therapy in Africa still widely varies with only 24% of children treated with antiretrovirals in 2013, while 64% of adults had access to these treatments [2]. HIV-infected children are also faced with several challenges with an impact on pediatric treatment compliance: poor and poorly educated family environment, lack of adequate pediatric formulations, lack of healthcare facilities with adequate human resources to prescribe and dispense drugs. Indeed, antiretroviral treatment effectiveness mainly depends on treatment compliance. Treatment compliance is defined as “the extent to which the patient’s behavior – taking medication, complying with dietary or lifestyle changes – is in line with the recommendations jointly agreed on with a healthcare professional” [7]. A continuous and high treatment compliance is required to suppress HIV viral replication, to improve the immune and clinical responses, to reduce the risk of developing resistance to antiretrovirals and of HIV transmission [8].

Since 2015, the World Health Organization (WHO) is recommending universal access to pediatric antiretroviral therapy [9] for all HIV-infected children as soon as diagnosis is established. In this context and considering the growing problem of antiretroviral resistance mutations [10], one must take treatment compliance into account to improve pediatric management strategies. The initial period of treatment initiation and the transition period from childhood to adolescence are key periods as they are associated with important risks of treatment failure due to a lack of compliance that may lead to the emergence of viral resistance. Preventing these failures and resistances is even more important in African countries located south of Sahara where second- and third-line therapeutic options are scarce. This literature review aimed to describe the main challenges of pediatric antiretroviral therapy compliance and to identify potential measures to improve compliance. The management of HIV-infected children in Africa will thus be improved.

2. What are the specificities of pediatric compliance with antiretroviral therapy?

Several difficulties related to therapeutic compliance are specific to the management of HIV-infected children.

Treatment of young infected children (usually younger than 12 years) depends on a caregiver, i.e. one of their parents, another family member, or anyone else. Treatment success therefore relies on the caregiver who needs to be highly involved, motivated, and concerned with compliance issues. Yet, caregivers may be confronted with compliance problems due to the child’s refusal to take the treatment or to their own busy schedule, which may result in treatment oversight [11,12]. Caregivers may also have a drinking or drug problem [13], or also be HIV-infected and preoccupied with their own health. Caregivers also tend to overestimate the child’s compliance with treatment [14]. Suboptimal management and care provided by caregivers therefore lead to a suboptimal care for the child.

Pharmaceutical forms of antiretrovirals are not always appropriate for children. Available syrup forms are difficult to dose and are often of bad taste. Syrup bottles are often big and cannot be easily concealed during transportation, which might lead to discrimination by family members or by the community [15]. Being afraid of discrimination is also an obstacle to good compliance, especially when the caregiver does not want other members of the family to be aware of the child’s HIV status. Antiretrovirals dispensed as tablets may also be too big and inappropriate for young children. They are also associated with a high number of pills to take or with dietary restrictions [16].

A 2008 recommendation mentions treating HIV-infected children as soon as possible to reduce the rates of early morbidity and mortality. Treatment should ideally be initiated at 6 weeks [8,12]. As antiretroviral therapy implies a life-long treatment, its long-term tolerability and efficacy, which depend on good compliance, are real concerns. As an almost perfect compliance is required in the long-term, treatment-induced fatigue may be a problem [17,18]. The continuous assessment of compliance is also associated with an important challenge as compliance is not a static phenomenon but a dynamic one with variations in time [19].

All these difficulties are even more severe in Sub-Saharan countries considering the poor healthcare environment: pediatric antiretroviral conservation, distribution, and dispense must be continuously ensured while few therapeutic options are available and countries are faced with many shortages of drugs.

3. Defining good compliance

As compliance is a dynamic phenomenon with variations in time, it is difficult to define a threshold according to which patients would be considered compliant or non-compliant. However, adult studies revealed that a compliance rate <95% of prescribed dose uptake was associated with poor immune response, increased risk of virological failure, and increased mortality rate [20,21]. This 95% threshold is also believed to be associated with increased resistance mutations, opportunistic infections, and

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