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Predictors of mortality among HIV-infected children receiving highly active antiretroviral therapy

Facteurs prédictifs de mortalité chez les enfants infectés par le VIH sous traitement antirétroviral hautement actif

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Abstract

Background and objectives. – The mortality rate of HIV-infected children can be reversed under highly active antiretroviral therapy (HAART). The impact of HAART on the mortality of HIV-infected children in Cameroon has not been extensively documented. We aimed to measure the mortality rate of HIV-infected children under HAART and to identify predictive factors of mortality.

Methods. – Retrospective cohort study of 221 children initiated on HAART from 2005 to 2009 and followed-up until 2013. Survival data was analyzed using Kaplan Meier method and Cox regression model to identify independent predictors of child mortality on HAART.

Results. – Overall, 9.9% of children ($n = 22$) died over a follow-up period of 755 child-years (mortality of 2.9 per 100 child-years); 70% of deaths occurred during the first six months of HAART. The probability of survival after four years of treatment was 88.7% (95% CI = [84.2–93.3]). During the multivariate analysis of baseline variables, we observed that the WHO clinical stages III and IV (HR: 3.55 [1.09–13.6] and HR: 7.7 [3.07–31.2]) and age ≤ 1 year at HAART initiation were independently associated with death (HR: 2.1 [1.01–5.08]). Neither orphanhood, baseline CD4 count or hemoglobin level nor low nutritional status predicted death in this cohort.

Conclusion. – The mortality of children receiving HAART was low after five years of follow-up and it was strongly associated with WHO stages III and IV and a younger age at treatment initiation.

Keywords: Children; HIV; HAART; Cameroon

Résumé

Contexte et objectifs. – La mortalité des enfants infectés par le VIH peut être inversée sous traitement antirétroviral hautement actif (TAHA). L'impact du TAHA sur la mortalité de ces enfants est faiblement rapporté au Cameroun. L'objectif était de mesurer le taux de mortalité des enfants infectés par le VIH traités par TAHA et les facteurs prédictifs de mortalité.

Méthodes. – Analyse de cohorte rétrospective sur 221 enfants ayant démarré le TAHA entre 2005 et 2009, et ayant été suivis jusqu'en 2013. Utilisation de la méthode de Kaplan-Meier et du modèle de Cox pour l'analyse de survie et pour l'identification des facteurs prédictifs de décès sous TAHA.

Résultats. – Parmi les 221 enfants, 9,9 % ($n = 22$) sont décédés au cours d'une période de suivi de 755 enfants-années (mortalité : 2,9 pour 100 enfants-années). Soixante-dix pour cent des décès sont survenus durant les six premiers mois de TAHA. La probabilité de survie après quatre ans de traitement était de 88,7 %. En analyse multivariée, les stades cliniques OMS 3 et 4 et l'âge ≤ 1 an à l'initiation du traitement étaient indépendamment associés au risque de décès. Le statut d'orphelin, le taux de CD4 et d'hémoglobine et le statut nutritionnel n'étaient pas prédicteurs de décès dans cette cohorte.

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Conclusion. – La mortalité sous TAHA était faible à 60 mois de suivi et fortement associée aux stades OMS 3 et 4 et au très jeune âge à l'initiation du TAHA.

Mots clés : Enfants ; VIH ; Traitement antirétroviral hautement actif ; Cameroun

1. Background

Approximately 3.3 million children under 15 years of age were living with HIV by the end of 2012. Most of them (90%) were from Sub-Saharan Africa. Only 650,000 of them were receiving highly active antiretroviral therapy (HAART) in low- and middle-income countries [1]. The benefit of early HAART on the survival and quality of life of HIV-infected children has been widely documented in historical cohorts of HIV-infected children from Western countries and Asia [2–5]. Mortality under HAART in Africa remains, on the other hand, quite high especially during the first six months following HAART initiation [6–8]. Many factors have been incriminated in the high mortality of HIV-infected children under treatment in Africa: poor nutritional status, WHO clinical stage, anemia, social and demographic data including maternal deaths. Cameroon is an endemic country for HIV. Access to HAART for infants has, however, been improved and almost 5000 HIV-infected children have been initiated on HAART from 2005 to 2013 (among 39,000 eligible patients) [9]. This national cohort is mainly being followed in four or five sites nationwide despite efforts for decentralization. In addition, the level of retention in care and the mortality rate on HAART is unknown. We aimed to measure the survival rate of children receiving HAART in Cameroon and to identify associated factors of child mortality in a pediatric antiretroviral therapy (ART) clinic.

2. Methods

2.1. Study site and population

We performed the study in the ESSOS Hospital of Yaoundé, Cameroon. This approved treatment center for ART is one of the two main pediatric ART clinics of the city. Pediatric HAART progressively started to be administered in this center as of the early 2000s. The program was then enhanced from 2005 onwards with the access to HAART free of charge nationwide. A total of 450 children have been initiated on HAART in this center since the start of the program.

2.2. Study design and data collection

We conducted a retrospective cohort study to analyze the survival rate and associated factors among children initiated on HAART between 2005 and 2009. Inclusion criteria included age ≤ 17 years, HIV-infected status on HAART, treatment initiation no later than January 2009, and patients still had to be followed at the study site. A total of 19 patients were excluded as they were transferred to another hospital. We included 221 children out of 450 (Fig. 1). Biological and clinical data at baseline and during follow-up were extracted from the clinical files. The primary endpoint was the rate of child mortality.

2.3. Clinical and biological procedures for follow-up and antiretroviral guidelines

Monthly follow-ups were scheduled for children receiving HAART during the first three months of treatment. Follow-up consultations were then scheduled quarterly. HAART was free of charge from the hospital pharmacy and was delivered on a monthly basis. Clinic services during the follow-up period were paid by patients. A supportive compliance program was offered to parents and children > 8 years of age. Early infant diagnosis using either real time PCR or qualitative PCR was performed at six weeks and later confirmed after nine months assuming a six week-delay following weaning for breastfed infants. The final diagnosis was established after 15 months. The final confirmation of the patient's HIV-negative status during the follow-up period was confirmed based on the following criteria: one negative virological test plus one negative serological test at or after 12 months, with a six week-delay following weaning for breastfed children. HIV infection was confirmed by two positive PCR at any time during follow-up, irrespective of the feeding mode, or by one positive serological test after 15 months.

2.4. Guidelines for antiretroviral treatment initiation followed in the study

The preferred first-line regimen for HIV-1-infected children and infants was non-nucleoside reverse-transcriptase inhibitors (NNRTIs) consisting of two nucleoside reverse-transcriptase inhibitors (NRTIs) and one NNRTI. The protocol was free of protease inhibitors assuming the mother did not receive any preventive treatment for mother-to-child transmission of HIV during pregnancy. Otherwise a protease inhibitor (PI)-based regimen was initiated. Efavirenz was the preferred NNRTI in children > 3 years of age, whereas nevirapine was prescribed to younger children. HAART was initiated during the follow-up period for all confirmed HIV-infected children < 1 year of age or classified as WHO stage III or IV irrespective of CD4 cell count.

2.5. Data collection

Data was routinely collected at the beginning of the follow-up period. A standard checklist was used for recording information from patient files into a form. The collection form included sociodemographic data, clinical and biological data at baseline