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Morbidity and healthcare resource utilisation in HIV-infected children following antiretroviral therapy (ART) initiation in Côte d'Ivoire, 2004–2009

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Abstract

Background—We describe severe morbidity and healthcare resource utilisation (HCRU) among HIV-infected children on antiretroviral therapy (ART) in Abidjan, Côte d'Ivoire.

Methods—All HIV-infected children enrolled in an HIV-care programme (2004–2009) were eligible from ART initiation until database closeout, death, ART interruption, or loss to follow-up. We calculated incidence density rates (IR) per 100 child-years (CY) for severe morbidity, HCRU (outpatient and inpatient care), and associated factors using frailty models with a Weibull distribution.

Results—Of 332 children with median age 5.7 years and median follow-up 2.5 years, 65.4% were severely immunodeficient by WHO criteria and all received cotrimoxazole prophylaxis. We recorded 464 clinical events in 228 children; the overall IR was 57.6/100 CY (95%CI: 52.1–62.5). Severe morbidity was more frequent in children on protease inhibitor-based ART compared to those on other regimens (aHR: 1.83, 95%CI: 1.35–2.47) and those moderately/severely immunodeficient compared to those not (aHR: 1.57; 95%CI: 1.13–2.18 and aHR: 2.53, 95%CI: 1.81–3.55 respectively). Of the 464 events, 371 (80%) led to outpatient care (IR: 45.6/100CY) and 164 (35%) to inpatient care (IR: 20.2/100CY). In adjusted analyses, outpatient care was significantly less frequent in children >10 years compared to children <2 years (aHR: 0.49, 95%CI: 0.31–0.78) and in those living furthest from clinic compared to those living closest (aHR: 0.65, 95%CI: 0.47–0.90). Both inpatient and outpatient HCRU were negatively associated with cotrimoxazole prophylaxis.

The authors declare not conflicts of interest.

Conclusion—Despite ART, HIV-infected children still require substantial utilization of healthcare services.

Keywords

HIV; children; antiretroviral therapy; morbidity; healthcare resource utilisation; West Africa

Introduction

Worldwide, approximately 2 million children live with HIV, 90% of whom live in sub-Saharan Africa (1). Most children acquire HIV via mother-to-child transmission (MTCT), and despite the scale-up of effective programmes aimed at preventing MTCT (PMTCT), the HIV epidemic continues to grow (1). In Côte d'Ivoire, an estimated 70,000 infants became newly infected with HIV in 2011 (1). Without antiretroviral therapy (ART), as many as 50% will die by their second birthday and 60% before age five (2, 3).

Since 2004, with the introduction of ART in Côte d'Ivoire, significant improvements in survival have been achieved (4, 5). However, the proportion of HIV-infected children who access ART remains unacceptably low, reaching only 15% in 2010 (1). Indeed, managing HIV infection in children is more difficult than in adults. First, providing a continuum of care between PMTCT and early infant diagnosis and ART remains a challenge (6–8) and many children fail to be diagnosed or treated despite their mothers being followed-up in HIV clinics. Second, diagnosis in children is complicated, requiring advanced and expensive PCR techniques, still not available on a routine basis (9). Finally, ART is a life-long and daily treatment, more difficult to manage in children, where paediatric formulations and dosages are not always available (10). For these reasons, scaling-up access to ART care in paediatric populations remains difficult in resource-limited settings (11, 12). Furthermore, despite the benefits of ART, HIV-infected children remain at risk for many other common infections and diseases that require healthcare (13, 14). Many studies in West Africa report increased survival of HIV-infected children on ART (4, 13–16), but few describe severe morbidity patterns and related utilization of healthcare. In this study we report severe morbidity and associated healthcare resource utilization (HCRU) in HIV-infected children on ART over the 2004–2009 scaling-up period in Abidjan, Côte d'Ivoire.

Methods

Settings and standard of care

The Aconda programme is a non-governmental association whose main objective is providing care to HIV-infected patients in Côte d'Ivoire. In partnership with the Bordeaux School of Public Health (ISPED, France), in 2004, Aconda launched a five-year programme of access to HIV care and ART according to the 2006 WHO guidelines. In addition to a number of public and private healthcare facilities, Aconda relies mostly on one dedicated paediatric care facility: the CePReF- (*Centre de Prise en Charge, de Recherche et de Formation*)- Enfant clinic. At CePReF, HIV-infected children are typically seen at least every three months, and CD4 counts are measured every 6 months; viral load is not routinely collected. ART, cotrimoxazole prophylaxis and blood analyses are free of charge. However, X-rays, in-patient day-care, and non-ART medications are only partially subsidized, while routine laboratory tests (blood smears, cultures, and microscopy) are still mostly paid for by patient families.

Study design and participants

This was a retrospective study conducted within a cohort of HIV-infected children followed-up within the CePReF facility in the Aconda care programme in Abidjan. All children under 15 years of age, with a medical record, who initiated ART for the first time between 1st January 2004 and 31st December 2009 after a confirmed HIV diagnosis, were included in the study. Children were followed from ART initiation until database closeout, death, ART interruption or loss to follow-up (no contact for >6 months), whichever came first.

Data collection

Patient data were collected retrospectively from paper-based medical records at CePReF, using a standardized data collection instrument issued specifically for this purpose. A thorough description of the data collection instrument has been described elsewhere (17). Severe morbidity was defined as any event classified as WHO stage 3 or stage 4, or any event leading to in-patient day-care, hospitalization, or death. Any similar event occurring within 30 days of the previous one was considered to be a complication and not counted as an additional event. Because there was no standard diagnosis validation tool, AIDS-defining events were defined according to the 2006 WHO case definitions of HIV surveillance (18). Malaria was defined as either definite, if confirmed by a positive blood smear, or probable, if a documented fever led to a prescription for an antimalarial drug. To be consistent within the study period, immunodeficiency was defined according to the WHO recommendations issued in 2006 (19).

Healthcare resource utilization (HCRU) was divided into two categories: *(i)* outpatient care, defined as either *(i.1)* a medical examination with a complementary diagnosis method (complete blood count, x-ray, or blood smear) or *(i.2)* any drug prescription other than cotrimoxazole prophylaxis or ART. *(ii)* Inpatient care, defined as either *(ii.1)* inpatient day-care by periods of 24 hours within the CePReF “day hospital” or *(ii.2)* hospitalization >24 hours at the University Hospital of Yopougon, Abidjan.

Statistical analyses

Baseline categorical data are presented as frequencies (percentage) and continuous variables using the median and interquartile range (IQR). Incidence rates (IR) of both severe morbidity and HCRU occurring per 100 child-years (CY) of follow-up were computed with their 95% confidence interval (95%CI). IRs were described overall and according to age at ART initiation and CD4% strata at time of event: >15%, 15 – 25 % and ≥25%.

To study the incidence of recurrent morbidity and recurrent HCRU rates since ART initiation, we used parametric frailty models, estimating the baseline hazard rates with a Weibull distribution. Frailty models are an extension of the Cox regression model; a frailty model is a random effect model for time-to-event data, accounting for intra-subject correlation (20, 21). Using shared frailty models allowed us to account for the dependence between recurrent events in a given patient. Moreover, children experiencing severe morbidity are more likely to die, either in hospital, or as several studies have shown, at home, unable to access care, and therefore are lost to follow-up (22). To account for this we also ran a joint frailty model, studying the joint evolution over time of two survival processes: the recurrent event (severe morbidity) and the terminal event (loss-to-programme), considering the latter as informative censoring (23). The dependence between the two processes was significant and hazard rates were computed for both the recurrent and terminal event. For HCRU, this association was not significant and we ran shared frailty models, accounting only for dependence between recurrent events (*i.e:* the probability for utilisation of healthcare services depended on having already used healthcare services previously). In all models we used the calendar timescale, where the start of the “at-risk”

period for each event was not reset to 0 after the previous event, but to the actual time since entry in the study, *ie* ART initiation. We used the package *frailtypack* of R statistical software version 2.15.2 (The R foundation for Statistical computing, Vienna, Austria), following guidelines presented by Rondeau *et al* (24).

Results

Baseline characteristics

Overall, 332 children initiated ART between 2004 – 2009 at the CePReF at median age at of 5.7 years (IQR: 2.6–9.3; Table 1). Of these, 54.8% were male and 29.1% were classified as CDC stage C; a significantly higher proportion of children aged ≥10 years were classified as CDC stage C compared to those aged <2 years (38.7%, p<0.0001). At ART initiation, all children were receiving cotrimoxazole prophylaxis. The median CD4% count at enrollment was 10.5% (IQR: 5.8–13.9), and 65.4% met the 2006 WHO criteria for immunodeficiency by age (19). The proportion of immunodeficient children was highest among children aged <2 years and aged 2–3 years, reaching 100% and 94.1% respectively in those age groups.

Follow-up

The median follow-up period was 2.5 years (IQR: 0.69–4.04). Overall, 45 (13.5%) children died and 22 (6.6%) were lost to follow-up. Ninety-nine children (30%) interrupted cotrimoxazole prophylaxis during follow-up, after a median time on ART of 1.8 years (IQR: 1.2–2.6); reasons for cotrimoxazole interruption were not documented. At ART initiation, 255 (77.3%) children initiated an NNRTI-based therapy, the remaining 75 (22.7%) initiated a PI-based ART regimen. During follow-up, 39 children (11.7%) switched to second-line treatment, defined as the change of class of treatment, at a median time of 1.7 years (IQR: 0.5–2.3). The reasons for switching to second-line were not documented; however we report one switch for toxicity, one for non-adherence, and two resulting from limited medication supply. Overall, the most common ART combinations for children on PIs were AZT+3TC +Nelfinavir (36%), d4T+3TC+Nelfinavir (32%) and ddI+ABC+Lopinavir/ritonavir (11%). Children on NNRTIs were most commonly on AZT + 3TC + Efavirenz (42%), d4T + 3TC + Efavirenz (32%) and AZT + 3TC + Nevirapine (11%).

Severe morbidity

During the study period, 228 (68.7%) children experienced severe morbidity, with a median number of 1 event per child (IQR: 0–3); the maximum number of severe events in a single patient was 8, and the total amount of events observed was 464. The median delay from ART initiation to occurrence of the first event was 2.3 months (IQR: 0.7–11).

The overall severe morbidity IR was 57.1 per 100 child-years of follow-up (CY) (95%CI: [52.1–62.5]). The global and CD4-strata specific IRs of selected clinical events by age group at ART initiation are given in Table 2. The overall IR was similar in children aged < and ≥5 years; however, we observed higher rates in children aged <5 years compared to ≥5 years when CD4% <25%. Event defining WHO stages 3 & 4 were the most common, with IRs reaching 82.9/100 CY in children <5 years with CD4 <15%. Non AIDS-defining morbidity was also substantial; in addition to malaria, dermatosis, asthma, otitis, parasitic diseases were the most commonly reported diseases. We observed high IRs of malaria and non AIDS-defining events, highest in children aged <5 years. Overall, the severe morbidity IR was highest within the first 6 months following ART initiation, and reduced considerably afterwards (Supplemental Digital Content (SDC) Table 1). We observed this trend when studying the specific IR of WHO 3/4 events; however, the IRs of tuberculosis, malaria and non-AIDS defining events IRs did not significantly differ over time (see SDC Table 1). We

observed 45 deaths, most from unknown causes (80%); only 8 deaths (17%) could definitely be attributed to an advanced stage of the disease.

In multivariate analyses, we observed a significant association between the incidence of recurrent severe morbidity and death or loss to follow-up. When adjusted for age, gender, ART regimen, and current CD4% strata, we observed a significant protective effect cotrimoxazole prophylaxis (adjusted HR [aHR]: 0.36; 95%CI: [0.23–0.56]). Children on a PI-based regimen were more likely to develop severe morbidity during follow-up (aHR: 1.83; 95%CI: [1.35–2.47]), as were children at more advanced stages of immunodeficiency (aHR: 1.57; 95%CI: [1.1 –2.18] and aHR: 2.53; 95%CI: [1.81 – 3.55] in moderately and severely immunodeficient children respectively; Table 3).

Healthcare resource utilization

Of the 464 severe morbid events, 411 (89%) led to at least one type of HCRU, either outpatient care (80%) or inpatient care (3.5%), yielding an estimated IR of any HCRU of 50.5 per 100 CY of follow-up (95%CI: 45.9–55.7) (Table 4).

Outpatient care IR was 45.6 per 100 CY (95%CI: [41.2–50.5]); medication prescription was the most frequent type of care provided, with a total of 651 different medications prescribed overall (IR: 80.1/100CY; 95%CI: 74.1–86.5]), mostly antibiotics (32%) and anti-malarials (11%). We observed significantly higher rates of antimalarial prescriptions in children <5 years old, consistent with observations made when studying severe morbidity, where higher rates of malaria were observed in this age group. We recorded 185 utilisations of complementary diagnoses, the IR was 22.8 / 100 CY (95%CI: 19.7 – 26.3]. Consequently, fewer than half of the documented severe morbidity had confirmed diagnoses: in the case of tuberculosis, only 50% underwent further examination, which in most cases was radiology; in the case of malaria, 62% of diagnoses were confirmed by further examination.

Table 5 presents multivariate analyses. When adjusted for gender, current CD4% strata, primary caregiver, and distance from the health clinic, we observed lower outpatient care in children aged >10 years (aHR: 0.49; 95%CI: [0.31–0.78]). Furthermore, children living beyond 20 kilometers from the clinic were less likely to utilize outpatient care (aHR: 0.65; 95%CI: [0.47–0.90]). Although outpatient care in children with CD4% between 15 and 25% did not differ significantly from those with CD4 >25%, we observed higher rates of outpatient care in the more immunodeficient children (aHR: 1.84; 95%CI: [1.32–2.56]), consistent with higher morbidity rates.

Utilization of inpatient care was much less frequent overall than outpatient care, despite the high rates of severe morbidity. The IR of inpatient day-care was 25.6/100CY (95%CI: [22.7–29.7]) and we observed only 17 hospitalisations (IR: 2.1/100CY; 95%CI: [1.3–3.4]). Hospitalisations occurred mostly when the disease required intra-venous treatment, such as anaemia (18%). In multivariate analyses (Table 5), inpatient care was more frequent in children who lived between 5–20 kilometres from the clinic compared to those who lived within the same district as the CePReF (aHR: 1.8; 95%CI:[1.05–3.11]). We also observed significantly lower hazards in children on cotrimoxazole prophylaxis (aHR: 0.29: 95%CI: [0.14–0.58]). There was a higher hazard of inpatient care in severely immunodeficient children (HR: 2.74; 95%CI: [1.58 – 4.78]), implying that severe morbidity led to this kind of care.

Overall, within in the first three months of ART initiation, we observed similar risks for severe morbidity and HCRU (SDC 2, which shows the baseline survival functions and confidence bands estimated by our frailty models for the probability of severe morbidity and

HCRU). After 3 months, survival without severe morbidity dropped significantly, while the risk for HCRU remained constant.

Discussion

This retrospective cohort study documents severe morbidity and associated healthcare resource utilization in HIV-1 infected children after ART initiation in Abidjan, Côte d'Ivoire. More than two thirds of the children included in our study developed at least one incident event during the follow-up period. Although most events were AIDS-defining and occurred within the first six months of ART, we also observed stable and substantial rates of non-AIDS defining events throughout the study period. In addition, overall severe morbidity was reduced by more than 60% in children who were on cotrimoxazole prophylaxis. Furthermore, although 88% of severe morbidity events did lead to utilization of some health care services, our findings reveal many missed opportunities for care.

Despite ART, we observed high rates of WHO stage 3/4 events within the first six months of ART initiation, which then decreased over time. Other studies have reported similar observations in resource-limited settings, attributing this trend to the early deaths of the sickest children and the benefits of ART for the remaining patients when children access to ART at advanced stage of the disease (25). Another plausible explanation is immune reconstitution inflammatory syndrome, likely manifesting in a number of mild or serious conditions (26). Furthermore, we believe that initiation of treatment at advanced stages of HIV disease and the slow rate of immune reconstitution with ART also play important roles. Indeed, the age distribution of our cohort (median age: 5.7 years) reflects the difficulties in early diagnosis of children in resource-limited settings and the many missed opportunities for early diagnosis and ART initiation. Consequently, children initiate ART at an advanced stage of immunodeficiency and, thus remain vulnerable to numerous severe opportunistic infections and infectious morbidity. Indeed, severe morbidity IRs were highest in those with lowest CD4% count, as in other studies in the African setting (13, 14, 25, 27). The overall tuberculosis IR was 1.7/100CY, and 4 times higher in severely immunodeficient children aged <5 years. Similar results were reported in a previous study in Abidjan in 2005 (28), but our observed rate is less than that reported in South Africa, where tuberculosis IRs reached 10/100CY (29). Although this may be due to a higher prevalence of tuberculosis disease in South Africa, we may also explain our findings by the lower access to tuberculosis diagnosis in the West African setting; this could underestimate the prevalence of tuberculosis in HIV-infected children (30). In addition, we also observed substantial IRs of malaria, particularly in children <5 years. The burden of malaria in this population is well documented (31, 32) but HIV therapies interact with antimalarial drugs making the management of malaria difficult (33). Our results reaffirm the importance of tuberculosis and malaria as pathogens in HIV-infected children on ART; these conditions need to be addressed in order to improve the care of HIV-infected children on ART.

ART regimen was another significant factor associated with recurrent severe morbidity, with higher risks for recurrent morbidity in children initiating PI-based ART, compared to those on NNRTIs. This could be an indicator bias caused by the fact that those initiating a PI-based regimen were those with more advanced disease, initiating second line treatment. Moreover, PI-based ART is more common in younger children, who could be more vulnerable to severe morbidity. However, our model adjusted for both age and second line treatment and therefore this confounding effect was limited. Another explanation could be the poor palatability and inconvenient formulation make adherence to lopinavir challenging in resource-limited settings.

AIDS-related diseases are not the only burden when managing post-ART care. Indeed, we observed, in our cohort, substantial IRs of non-AIDS defining morbidity that did not decrease over time. The lack of resources for prevention, diagnostic tools and management of general morbidity in the African setting is a strong barrier to the establishment of effective HIV care programmes. Nevertheless, we reported that cotrimoxazole prophylaxis had a significant effect in reducing severe morbidity over and above the ART-effect. This observation is consistent with previous studies, describing the field effectiveness of this kind of prophylaxis (34–36). While prior studies may question the role of cotrimoxazole prophylaxis after starting ART (37), we note that, in this context, while children continue to initiate ART at advanced stages of the disease and are vulnerable to opportunistic infections and infectious morbidity, cotrimoxazole prophylaxis reduces morbidity and mortality in HIV-infected children (38, 39). Furthermore, we observed that utilization of both outpatient and inpatient care was negatively associated with the use of cotrimoxazole prophylaxis, which supports our previous statement: cotrimoxazole prophylaxis reduces severe morbidity, and thus healthcare resource utilization. Efforts in scaling up access to such prophylaxis must continue, even in ART-treated children.

Overall, 89% of the severe morbidity in our study led to medical examinations or treatment, which is higher than that observed in pre-ART cohorts (40). Despite this apparently high proportion, our observations underline the need for more effective care and management of HIV-related diseases. Indeed, resources for diagnosis and treatment have become available through HIV/AIDS control programmes, facilitating patient utilization of healthcare services. In particular, use of complementary diagnoses remained low. We hypothesize that costs are the major explanation for the gap we observed between severe morbidity and HCRU. For example, the lack of use of diagnostic tools can be attributed to the high costs for patients' families when non-subsidized or more elaborate examinations are required. In addition, outpatient care was less frequent in children living beyond 20 kilometers from the clinic; we anticipate that the cost of transport to the clinic is a considerable factor in this observation. Similarly, in-patient day-care at the CePReF is subsidized, whereas hospitalizations are not. Consequently, many patients opt for 3 or 4 consecutive days of inpatient day-care, returning home every evening, rather than hospitalization, thus delaying care.

In addition to costs, social stigmatization may also explain many missed opportunities for care (41). HIV-related stigma and discrimination continue to be present in every country and region of the world, creating major barriers to providing adequate care, support and treatment. We observed lower use of inpatient care in children living within the clinic's district compared to those living beyond 10 kilometers. Indeed, the clinic being in their neighbourhood, families may be afraid of stigma if seen attending an HIV clinic on a daily basis.

This study has several limitations. First, the age distribution of our cohort raises the question of a left-truncation bias: HIV-infected children <2 years of age usually have rapidly progressive disease with high mortality (2), and the less symptomatic children are the ones most likely to survive until late ART initiation. Therefore, our study is mostly based on a population of "survivors," comprised of children with either a less rapidly progressive disease, or who may have benefitted from prior healthcare support offered outside of the Aconda context. Second, the morbidity and HCRU data used in this study were collected retrospectively and may have resulted in underestimations of the true incidence of morbidity. Furthermore, practices may vary over time and between paediatricians, influencing the frequencies of routinely confirmed diagnoses. However, we attempted to ensure the accuracy of diagnosis by requiring all specific documentation from medical charts (clinical findings, laboratory examinations, radiographic results or copies of

prescriptions). Third, our data may be incomplete on other levels: anthropometric data were scarce, preventing assessment of malnutrition (13). Furthermore, we have no data on adherence and hence are unable to ascertain if the children presenting the most events were not taking their treatment as recommended. Fourth, the lack of comparable pre-ART data collection prevented the comparison of incidence rates before and after treatment and the assessment of the extent to which the declining incidence rates of severe morbidity that we observed were due to ART and/or care effects. Finally, although we adjusted for loss to programme in our analyses, we are unable to ascertain events among children not in care, and thus likely underestimated true IRs. Indeed, it is not uncommon for children to skip visits and consequently many severe morbid events may go unnoticed by the paediatrician. Furthermore, since good clinical outcomes depend essentially on treatment adherence, when untreated, these events are liable to lead to other comorbidities and/or death, contributing to the underestimations of our IRs. However, this limitation exists also in many other studies, which demonstrate comparable loss-to-follow-up rate (14, 25, 42). In the light of this trend, expanding an earlier access to ART is essential to avoid severe comorbidities in HIV-infected children. Evidence for strategies to improve access and adherence to ART for children and adolescents is lacking, however, several studies have demonstrated the benefits of decentralized HIV/AIDS and task –shifting such as nurse-initiated and managed ART(43, 44). A recent study in Rwanda reported that providing ART to children in a health center/ nurse-based programme is both feasible and very effective (45).

Despite these limitations, our study provides original data on severe morbidity and healthcare resource utilization in Côte d'Ivoire for ART-treated children during a period of service scale-up, reflecting the clinical practices in this setting. Caring for children with HIV remains challenging where the burden of non AIDS-related diseases is high. Because of operational limitations such as delays in diagnosis or presentation to care and the requirement for self-pay for a number of diagnostic and therapeutic services, we observed many missed opportunities for care (46). Cotrimoxazole prophylaxis appears to continue reduce severe morbidity and thus healthcare resource utilization in ART-treated children. Younger children are particularly vulnerable to severe morbidity despite ART, underscoring the urgent need for early identification, rapid treatment initiation, and long term retention in care, including close monitoring, improved diagnostics, and treatment for comorbidities. Improving post-ART care remains a priority in the management of the paediatric HIV epidemic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of the 332 HIV-infected children initiating ART and followed-up at the CePReF between 2004 – 2009, Abidjan, Côte d'Ivoire.

	Overall N = 332	*< 2 years* N = 62	*2 – 3 years* N = 34	*3 – 5 years* N = 52	*5 – 10 years* N = 109	*> 10 years* N = 75
Age, years, median (IQR)	5.7 *(2.6 – 9.3)*	1.3 *(0.9 – 1.8)*	2.5 *(2.2 – 2.7)*	4.0 *(3.6 – 4.5)*	7.1 *(6.3 – 8.4)*	12.2 *(11.0 – 14.3)*
Male,n (%)	182 *(54.8)*	34 *(54.8)*	21 *(61.8)*	33 *(63.5)*	49 *(45.0)*	45 *(60.0)*
CD4 cell % median (IQR)	10.5 *(5.8 – 13.9)*	14.3 *(10.2 – 17.7)*	12.5 *(7.8 – 14.2)*	10.9 *(6.3 – 13.5)*	8.4 *(2.2 – 12.4)*	8 *(3.6 – 12.9)*
CD4 count/µL,median (IQR)	293 *(96 – 614)*	785 *(518 – 1070)*	587 *(403 – 1082)*	394 *(220 – 603)*	162 *(33 – 333))*	135 *(33 – 273)*
Imunnodeficient* children, n (%)	217 *(65.4)*	62 *(100.0)*	32 *(94.1)*	12 *(23.1)*	60 *(55.1)*	51 *(68.0)*
CDC Stage C	96 *(29.1)*	19 *(31.2)*	8 *(2.35)*	14 *(26.9)*	26 *(24.1)*	29 *(38.7)*
Cotrimoxazole prophylaxis, n (%)	332 *(100.0)*	62 *(100.0)*	33 *(97.1)*	51 *(98.1)*	108 *(99.1)*	75 *(100.0)*
Antiretroviral regimen						
NNRTI	255 *(77.3)*	38 *(61.3)*	15 *(44.1)*	39 *(75.0)*	93 *(86.9)*	70 *(93.3)*
PI	75 *(22.7)*	24 *(38.7)*	19 *(55.8)*	13 *(25.0)*	14 *(13.1)*	5 *(6.7)*
Principal caregiver. n (%)						
Mother alone	65 *(19.6)*	13 *(21.0)*	9 *(26.5)*	11 *(21.2)*	23 *(21.1)*	9 *(12.0)*
Father alone	33 *(9.9)*	3 *(4.8)*	5 *(14.7)*	3 *(5.8)*	15 *(13.8)*	7 *(9.3)*
Both parents	129 *(38.7)*	39 *(62.9)*	17 *(50.0)*	34 *(65.4)*	26 *(23.9)*	13 *(17.3)*
Other	105 *(39.2)*	7 *(11.3)*	3 *(8.8)*	4 *(7.7)*	45 *(41.3)*	46 *(44.2)*
Distance from clinic, n(%)						
< 5 kms	186 *(56.0)*	45 *(72.6)*	19 *(55.9)*	32 *(61.5)*	50 *(45.9)*	40 *(53.3)*
5 – 20 kms	67 *(20.2)*	8 *(12.9)*	9 *(26.5)*	8 *(15.4)*	19 *(17.4)*	23 *(30.7)*
> 20 kms	79 *(23.8)*	9 (14.5)	6 *(17.7)*	12 *(15.2)*	40 *(36.7)*	12 *(16.0)*

*According the 2006 WHO definitions

Table 2

Incidence rates of overall severe morbidity by CD4% strata during follow-up in the 332 HIV-infected children initiating ART and followed-up at the CePReF between 2004 – 2009. Abidjan. Côte d'Ivoire

	Global		CD4% strata								
			< 15% (326.93 CY)			15 – < 25% (247.06 CY)			≥25% (239.17 CY)		
	IR*	*95%CI*	N	IR*	*95%CI*	N	IR*	*95%CI*	N	IR*	*95%CI*
Overall	57.1	*[52.1 – 62.5]*	265	110.8	*[98.3 – 125.0]*	108	43.7	*[36.2 – 52.3]*	91	27.8	*[22.7 – 34.2]*
WHO Stage 1&2	0.6	*[0.3 – 1.4]*	1	0.4	*[0.1 – 2.3]*	2	0.8	*[0.3 – 2.9]*	2	0.6	*[0.2 – 2.2]*
WHO Stage 3&4	38.5	*[34.5 – 43.0]*	182	76.1	*[65.8 – 88.0]*	71	28.7	*[22.8 – 36.3]*	60	18.4	*[14.3 – 23.6]*
Tuberculosis	1.7	*[1.0 – 2.9]*	11	4.6	*[2.6 – 8.2]*	2	0.8	*[0.3 – 2.9)*	1	0.3	*[0.1 – 1.7]*
Malaria	8.7	*[6.9 – 11.0]*	29	12.1	*[8.5 – 17.4]*	21	8.5	*[5.6 – 13.0]*	21	6.4	*[4.2 – 9.8]*
Non AIDS defining	6.9	*[5.3 – 8.9]*	38	15.9	*[11.6 – 21.8]*	11	4.5	*[2.5 – 8.0]*	7	2.1	*[1.1 – 4.4]*
< 5 years											
Overall	57.8	*[50.8 – 65.8]*	93	124.3	*[101.5 – 152.3]*	81	63.7	*[51.3 – 79.2]*	57	28.9	*[22.3 – 37.4]*
WHO Stage 1&2	1	*[0.4 – 2.6]*	1	1.3	*[0.3 – 7.5]*	2	1.6	*[0.5 – 5.7]*	1	0.5	*[0.1 – 2.8]*
WHO Stage 3&4	36.8	*[31.3 – 43.2]*	62	82.9	*[64.7 – 106.2]*	52	40.9	*[31.2 – 53.6]*	33	16.7	*[11.9 – 23.4]*
Tuberculosis	2,0	*[1.0 – 3.9]*	6	8,0	*[3.8 – 17.5]*	2	1.6	*[0.5 – 5.7]*	0	-	-
Malaria	12,0	*[9.1 – 15.9]*	13	17.4	*[10.2 – 29.7]*	17	13.4	*[8.4 – 21.4]*	18	9.1	*[5.8 – 14.4]*
Non AIDS defining	5.3	*[3.5 – 8.0]*	9	12,0	*[6.4 – 22.8]*	7	5.5	*[2.7 – 11.3]*	5	2.5	*[1.1 – 5.9]*
≥ 5 years											
Overall	56.4	*[49.6 – 64.1]*	172	104.6	*[90.2 – 121.5]*	27	22.5	*[15.5 – 32.8]*	34	26.3	*[18.9 – 36.8]*
WHO Stage 1&2	0.3	*[0.1 –1.4]*	0	-	-	0	-	-	1	0.8	*[0.2 – 4.3]*
WHO Stage 3&4	40.6	*[34.9 – 47.3]*	121	73.6	*[61.7 – 87.8]*	19	15.9	*[10.2 – 24.8]*	28	21.7	*[15.0 – 31.3]*
Tuberculosis	1.5	*[0.7 – 3.2]*	5	3,0	*[1.3 – 7.1]*	0	-	-	1	0.8	*[0.2 – 4.3]*
Malaria	5.6	*[3.7 – 8.4]*	16	9.7	*[6.0 – 15.8]*	4	3.3	*[1.4 –8.5]*	3	2.3	*[0.8 – 6.8]*
Non AIDS defining	8.5	*[6.1 – 11.8]*	29	17.7	*[12.3 – 25.3]*	4	3.3	*[1.4 – 8.5]*	2	1.6	*[0.5 – 5.6]*

* IR: Incidence rate

Table 3

Determinants of severe morbidity among the 332 HIV-infected children on ART, followed-up at the CePReF between 2004–2009. Abidjan. Côte d'Ivoire. Joint Frailty adjusted model with estimated adjusted hazard ratios (aHR) and 95%CI

	aHR	*IC95%*	*p*
For recurrences (severe morbidity)			
Age at ART initiation			*0,793*
< 5 years	1	–	
≥ 5 years	1,04	*[0,77 – 1,41]*	
Cotrimoxazole	0,36	*[0,23 – 0,56]*	*<0,001*
CD4 %			*<0,001*
< 15%	1	–	
15 – 25 %	1,57	*[1,13 – 2,18]*	
≥ 25%	2,53	*[1,81 – 3,55]*	
Gender: Male/Female	1,04	*[0,79 – 1,37]*	0,947
ART regimen			*<0,001*
NNRTI	1	–	
PI	1,83	*[1,35 – 2,47]*	
Second line treatment	0,68	*[0,42 – 1,12]*	*0,127*
For survival			
Age at ART initiation			*0,626*
< 5 years	1	–	
≥ 5 years	0,85	*[0,45 – 1,61]*	
Cotrimoxazole	2,52	*[0,81 – 7,87]*	*0,111*
CD4 %			
< 15%	1	–	*<0,001*
15 – 25 %	2,11	*[0,76 – 5,87]*	
≥ 25%	8,30	*[3,18 – 21,65]*	
Variance of random effect, (SE)		0,77 (0,11)	*< 0,001*
α* (SE)		1,13 (0,33)	*< 0,001*

*When α = 1, the effect of the frailty is identical for the recurrent events and the terminating event. When α > 1, the recurrent rate and the survival rate are positively associated.

Table 4

Incidence rates of healthcare resource utilization (outpatient and inpatient care) by age at ART initiation during follow-up in the 332 HIV-infected children followed-up at the CePReF between 2004 – 2009. Abidjan. Côte d'Ivoire

			Age at ART initiation					
			< 5 years (399.69 CY)			≥ 5 years (413.48 CY)		
	IR*	*95%CI*	N	IR*	*95%CI*	N	IR*	*95%CI*
Overall†	50.5	*[45.9 – 55.7]*	214	53.5	*[46.8 – 61.2]*	197	47.6	*[41.5 – 54.8]*
Outpatient care †	45.6	*[41.2 – 50.5]*	196	49.0	*[42. 7 – 56.4]*	175	42.3	*[36.5 – 49.1]*
Complementary diagnoses	22.8	*[19.7 – 26.3]*	94	23.5	*[19.2 – 28.8]*	91	22.0	*[17.9 – 27.0]*
Prescribed medication	80.1	*[74.1 – 86.5]*	345	86.3	*[77.7 – 95.9]*	306	74.0	*[66.2 – 82.8]*
Antiobiotics	25.7	*[22.5 – 29.4]*	104	26.0	*[21.5 – 31.5]*	105	25.4	*[20.1 – 30.7]*
Antimalarials	8.9	*[7.0 – 11.2]*	48	12.0	*[9.1 – 15.9]*	24	5.8	*[3.9 – 8.6]*
TB treatment	1.7	*[1.0 – 2.9]*	8	2.0	*[1.0 – 3.9]*	6	1.5	*[0.7 – 3.2]*
Inpatient care †	20.2	*[17.3 – 23.5]*	87	21.8	*[17.7 – 26.9]*	77	18.6	*[14.9 – 23.3]*
Daycare (24 hours)	25.6	*[22.7 – 29.7]*	117	29.3	*[24.4 – 35.1]*	94	22.7	*[18.6 – 27.8]*
Hospitalisations	2.1	*[1.3 – 3.4]*	8	2.0	*[1.0 – 3.9]*	9	2.2	*[1.2 – 4.1]*

*Incidence rate,

†At least one of the below

Table 5

Estimated hazard ratios and 95%CI for factors associated with HCRU during follow-up in the 332 HIV-infected children followed-up at the CePReF between 2004 – 2009. Abidjan. Côte d'Ivoire. Shared Frailty Models.

	Outpatient care			Inpatient care		
	HR	***IC95%***	***P***	**HR**	***IC95%***	***P***
Age at ART initiation			*0.028*			*0.895*
<2 years	1	–		1	–	
2–3 years	0.84	*[0.51 – 1.25]*		0.91	*[0.42 – 2.00]*	
3 – 5 years	0.95	*[0.64 – 1.41]*		1.06	*[0.53 – 2.09]*	
5 – 10 years	0.84	*[0.57 – 1.23]*		0.9	*[0.46 – 1.77]*	
≥ 10 years	0.49	*[0.31 – 0.78]*		0.72	*[0.33 – 1.55]*	
Gender: Male/Female	1.02	*[0.79 – 1.32]*	*0.95*	0.82	*[0.54 – 1.25]*	*0.498*
Caregiver			*0.458*			*0.106*
Both parents	1	–		1	–	
Mother alone	1.06	*[0.76 – 1.48]*		0.96	*[0.54 – 1.71]*	
Father alone	0.67	*[0.40 – 1.12]*		0.34	*[0.13 – 0.87]*	
Other	1.14	*[0.80 – 1.62]*		1.08	*[0.60 – 1.96]*	
Distance from clinic			*0.042*			*0.018*
> 5 kms	1	–		1	–	
5 – 20 kms	0.97	*[0.70 – 1.35]*		1.8	[1.05 – 3.11]	
≥ 20 kms	0.65	*[0.47 – 0.90]*		0.69	[0.39 – 1.23]	
CD4 %			*< 0.001*			*<0.001*
≥ 25%	1	–		1	–	
15 – 25 %	1.2	*[0.86 – 1.66]*		1.58	*[0.92 – 2.72]*	
< 15%	1.84	*[1.32 – 2.56]*		2.74	*[1.58 – 4.78]*	
Cotrimoxazole	0.34	*[0.21 – 0.53]*	*<0.001*	0.29	*[0.14 – 0.58]*	*<0.001*
Variance of random effect, (SE)		0.33 (0.10)	*< 0.001*		1.23 (0.35)	*<0.001*