Programmatic Impact of the Evolution of WHO Pediatric Antiretroviral Treatment Guidelines for Resource-Limited Countries (Tukula Fenna Project, Uganda)

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Background: World Health Organization (WHO) recommendations for the initiation of antiretroviral therapy (ART) in children were revised in 2010, but the programmatic impact has had limited study.

Methods: We used a cohort of 985 Ugandan children followed since 2003 by the Tukula Fenna project to model the differential impact of the 2006, 2008, and 2010 WHO pediatric ART initiation criteria on the proportion of children eligible for ART at enrollment and over time.

Results: Using the WHO 2006, 2008, and 2010 ART criteria, 40%, 57%, and 66% of children, respectively, would have been eligible for ART at enrollment and 76%, 84%, and 88% 2 years later. Evaluating the entire cohort followed for 6 years using the 2006, 2008, and 2010 guidelines, the proportion in need of ART was found to be 70%, 82%, and 87%, respectively. Between 2006 and 2008, the proportions of eligible children starting ART within 6 and 12 months were 39% and 50%, respectively; after this, the proportions starting within 6 and 12 months were 50% and 52%. Before 2008, the most common criterion met in children who did not start ART was WHO clinical stage (odds ratio = 2.0, CI 95% = 1.2 to 3.2); after the 2008 recommendations, the most common eligibility criterion in children who did not start ART was age <12 months (odds ratio = 10.5, CI 95% = 3.8 to 31.1).

Conclusions: An overall increase of 17% (from 70% to 87%) in children in need of ART was observed in our cohort comparing the 2006 and 2010 guidelines; this increase was primarily driven by the introduction of universal treatment for infants <12 months in 2008.

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INTRODUCTION

Human immunodeficiency virus (HIV) infection in infants is rapidly progressive and is often a fatal disease. Infected infants frequently present with clinical symptoms in the first year of life; in resource-limited settings, without effective therapy, by age 1 year, an estimated one-third of infected infants will have died and by age 2 years, over half will have died.[1] In resource-rich countries, early initiation of effective antiretroviral therapy has transformed HIV infection into a chronic disease, with the survival of HIV-infected infants and children into adolescence and adulthood.[2] In the United States, well over 90% of HIV-infected children are receiving antiretroviral therapy.[3]

The World Health Organization (WHO) publishes guidelines for the treatment of pediatric HIV infection in resource-limited countries based on a public health approach, using standardized and simplified antiretroviral regimens that offer both a durable response and preserve future treatment options based on the best available scientific evidence. WHO pediatric guidelines were first published in 2004 combined with the guidelines for adults; in 2006, stand-alone guidelines for children were published. Given rapidly evolving evidence of the optimal time to start therapy in children in resource-limited settings, the criteria for initiation of treatment were revised and expanded in 2008 and 2010.

However, only 23% of children who need treatment are accessing it.[4] Significant obstacles to scaling up pediatric care remain, including limited screening for HIV, lack of access to virological testing for early infant diagnosis, lack of human capacity, and lack of affordable and manageable pediatric antiretroviral drug formulations. As a result, health care systems in resource-limited countries are struggling to meet the demands of national pediatric treatment.

The Guidelines for treatment initiation are based on age, WHO clinical stage, and immune status. In 2006, the treatment guidelines were more complex: treatment was recommended for all children with WHO stage 4 disease regardless of CD4 count; all infants <12 months with

WHO stage 3 disease, regardless of CD4 count, and all older children with the exception of those who met WHO stage 3 disease based on tuberculosis, oral hairy leukoplakia, lymphoid interstitial pneumonia, or thrombocytopenia, where CD4 was recommended for decision making if available; treatment of WHO stage 1 or 2 disease was recommended only if CD4 count was available; 4 age-related CD4 treatment thresholds were used (<11 months; 12–36 months; 36–59 months; >5 years). In 2008, based on clinical trial data demonstrating that initiation of treatment at age <12 weeks significantly improved survival,[5] the guidelines were modified to recommend treatment for all infants who are <12 months regardless of WHO clinical stage or CD4 count. In 2010, these criteria were further broadened to recommend therapy for all children age <24 months; all children with WHO clinical stage 3 or 4 disease, regardless of CD4 count; for children >24 months with WHO stage 1 or 2 disease, CD4 criteria were simplified into 2 age-related categories (24–60 months and >5 years), and the CD4 threshold for initiation of treatment was increased.

We used data from a Ugandan cohort of HIV-infected infants accessing care in the urban district of Kampala to assess the impact of the changing WHO pediatric guidelines on the number of children in need of treatment and to estimate the degree of guidelines implementation achieved within the program.

METHODS

Data from a cohort of HIV-infected children followed since January 2003 by the Tukula Fenna project (St Francis of St Raphael Hospital, Kampala—Uganda[6]) were analyzed. Children are enrolled in the program from a variety of points of entry, including programs to prevent mother-to-child transmission, outpatient and inpatient services. HIV is diagnosed by HIV–DNA–polymerase chain reaction in infants <18 months or by HIV-antibody testing in those ≥18 months. Patients are followed with monthly clinical examinations and laboratory monitoring (CD4 count/percent, full blood count, and liver function tests, amylase, and creatinine) at baseline and every 6 months. Cotrimoxazole prophylaxis, psychosocial and nutritional support are also provided.

To evaluate the impact of serial WHO guidelines revisions on the proportion of children eligible for ART, treatment initiation criteria recommended by WHO 2006,[7] 2008,[8] and 2010[9] pediatric treatment guidelines were independently applied to the same cohort over time. Children were followed from enrollment and censored at the time they first met the different WHO treatment criteria or if lost to follow-up (defined as a child not seen for >6 months since the last visit) or dead. The cumulative proportion of patients becoming eligible for treatment was calculated, and Kaplan Meier method was used to estimate the probability of becoming treatment eligible over time after enrollment in the program.

WHO criteria became more comprehensive over time allowing for an earlier initiation of treatment, and thus, a child who was eligible according 2006 criteria would also be eligible based on the 2008 and 2010 criteria. The overall proportion of patients becoming eligible for treatment during follow-up was considered for each WHO set of criteria and reasons for becoming ART eligible (eg, age, WHO clinical stage, or CD4 count/percentage) were separately examined.

To estimate the actual implementation of the guidelines in the program, we assessed the proportion of children starting treatment as recommended. Two periods of time were defined on the basis of the treatment initiation criteria being used: the first from January 2006 when ART became widely available in Uganda until July 2008 when universal treatment for infants was recommended by WHO, and the second from July 2008 until of July 2009 (data freeze).

RESULTS

The cohort included 985 children and a total of 1899.55 persons per year of follow-up; 483 (49%) were male and 492 female, with a median age at enrollment of 5.8 years (interquartile range 1.7–10.1). The median baseline CD4% was 13.7% (interquartile range 7.1%–21.8%), and 63.6% of patients presented with symptomatic disease (45.9% WHO stage 2, 13.9% WHO stage 3, and 3.8% WHO stage 4).

According to the 2006, 2008, and 2010 WHO criteria, 40%, 57%, and 66% of the children, respectively, were already eligible for treatment at the time of enrollment, and by 2 years from enrollment, the probability of being eligible for treatment increased to 76%, 84%, and 88%, respectively (Fig. 1 and Table 1).

By applying 2006, 2008, and 2010 WHO guidelines during the 6 years of observation, the number of children in need of treatment in the cohort increased from 693 to 806 up to 857, respectively (Fig. 2). Overall, a 17% increase in the total number of patients requiring initiation of treatment was observed when applying 2010 guidelines as compared with the 2006 criteria, and 5% more comparing the 2010 with 2008 guidelines (Fig. 2).

Of those eligible for treatment, 21% of children met the 2008 eligibility criteria (when universal treatment for infants

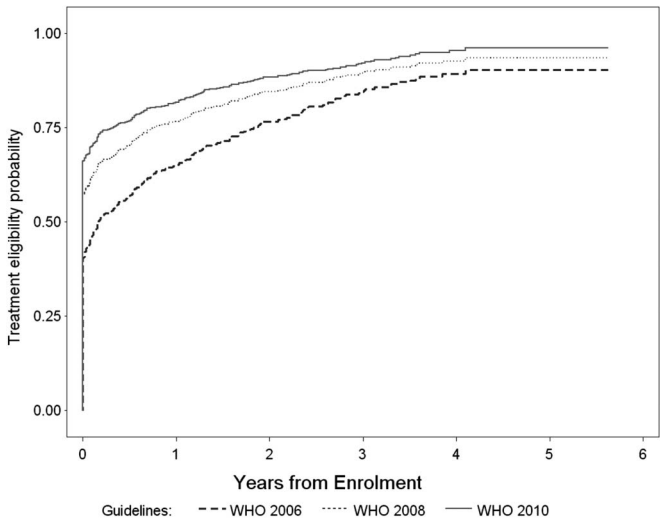

FIGURE 1. Probability of becoming eligible for treatment over time from enrollment.

TABLE 1. ART Eligible Children at Enrollment and After 2 Years of Follow-Up

Guidelines	Children ART Eligible Overall	Children ART Eligible at Enrollment	Probability to be ART Eligible at 2 Yrs (CI 95%)
WHO 2006	693 (70%)	397 (40%)	76% (73% to 80%)
WHO 2008	806 (82%)	562 (57%)	84% (82% to 87%)
WHO 2010	857 (87%)	650 (66%)	88% (86% to 91%)

<12 months was recommended) secondary to age criteria. This proportion increased to 32% in 2010, when the age threshold for universal therapy was raised to 24 months.

Using the 2006 treatment guidelines, 49% of children met the eligibility for treatment secondary to WHO clinical staging criteria while using the 2008 and 2010 guidelines, 26% and 28%, respectively, met treatment criteria due to WHO clinical stage criteria. CD4 criteria accounted for treatment eligibility in 51%, 43%, and 40% of children in 2006, 2008, and 2010.

Twelve percent of infants and 26% of those <2 years who would have been eligible for treatment based on age criteria in the 2008 and 2010 guidelines, respectively, also had clinical or immunological criteria that met the 2006 treatment thresholds at the time of enrollment. Out of the remaining 148 (88%) and 205 (74%) children eligible for treatment solely due to their age in 2008 and 2010, respectively, 25% and 30% showed subsequent disease progression and met the clinical or age-specific immunological criteria for treatment by the end of the observation time.

From 2006 to 2008, the proportions of children potentially eligible for treatment who actually started treatment within 6 and 12 months based on the existing treatment guidelines were 39% and 50%, respectively; after 2008, the proportion starting within 6 and 12 months of eligibility was 50% and 52%, respectively (Table 2). In the period before 2008, 20% of children overall did not start treatment despite meeting eligibility criteria for treatment; in the period after 2008, 25% of children did not start treatment despite being eligible (Fig. 3). Before 2008, the most common eligibility

TABLE 2. Children Initiating ART Within 6 and 12 Months From Meeting Eligibility Criteria

Effective ART Initiation	WHO 2006	WHO 2008
Within 6 mos from eligibility	139/355 (39%)	51/101 (50%)
Within 12 mos from eligibility	178/355 (50%)	53/101 (52%)

criteria met in children who did not start treatment was WHO clinical stage criteria (odds ratio = 2.0, 95% CI = 1.2 to 3.2); after 2008, the most common eligibility criteria met in children who did not start treatment was age <12 months (odds ratio = 10.5, 95% CI = 3.8 to 31.1).

DISCUSSION

The programmatic impact of adopting 2010 WHO pediatric guidelines for starting treatment is still unknown, and there are concerns that the expanded treatment recommendations will significantly increase the workload in already overburdened programs. We described the potential scenario that programs may encounter after implementation of the new recommendations. Comparing 2006 guidelines with 2010, an overall increase of 17% (from 70% to 87%) of children in need for treatment was observed over 6 years of follow-up in our cohort. However, this rise was primarily driven by the introduction of universal treatment for infants already recommended in 2008.

In cohorts with similar characteristics, the recommendation for universal treatment for children under 2 years is expected to increase the number of patients who are already eligible for treatment at the time of enrollment as compared with using only clinical and immunological criteria by 65% (from 40% to 66%) (Fig. 1). However, the age at enrollment in our cohort (5.8 years) is relatively old. Ideally, pediatric treatment services would be linked to the prevention of mother-to-child services and ensure early identification of HIV exposure and diagnosis of infection, allowing HIV-infected children to start treatment as infants. In contrast to our findings, such a program would be significantly affected

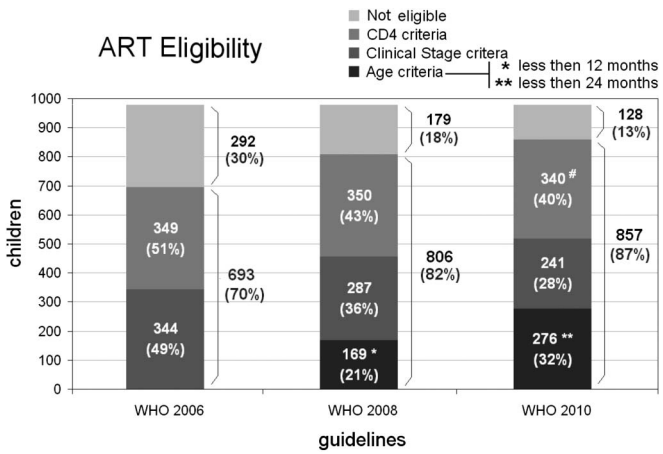

FIGURE 2. Proportion of children in need of treatment and reasons for eligibility (2003–2009).

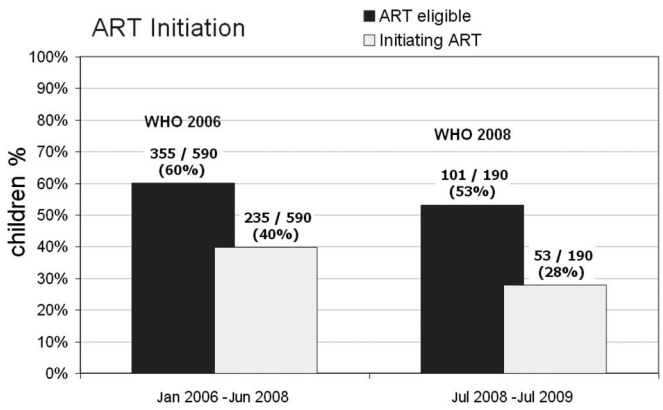

FIGURE 3. Proportion of children who are ART eligible and initiating treatment according to the guidelines being adopted in the cohort over time (2003–2009).

by the 2008 treatment recommendation for all children under age 1 year but much less affected by the 2010 extension of treatment to all children under age 2 years. Our findings highlight the existing gaps in early infant diagnosis and missed opportunities for treatment that still exist for children globally.

Because patients were more likely to present with advanced disease in the earliest years of the Tukula Fenna program, differences in baseline characteristics and calendar year of enrollment should be taken into consideration and caution should be exercised when applying our estimates to other settings.

In this cohort, only half of treatment-eligible children were started on antiretroviral therapy within 12 months of the time they met eligibility criteria. A significant delay in treatment initiation was observed, highlighting the need for a prompt clinical and immunological assessment, faster CD4 results turnaround time, and a streamlining pretreatment counseling process.

In conclusion, we believe that to achieve a successful implementation of a new standard for treatment initiation in children, additional efforts will be needed to ensure that infants and young children are initiated on treatment in a timely manner. In this context, strengthening of early infant diagnosis services and the dissemination of the new guidelines are critical.

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