Timing of antiretroviral therapy in children with advanced HIV

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AIDS-related mortality in children fell by almost half between 2010 and 2016 as a result of declines in new infections and greater access to antiretroviral therapy (ART).[1] ART is now recommended for all children regardless of clinical or immunological stage;[2] however, many still remain unidentified and present with severe immunosuppression, particularly in sub-Saharan Africa.[3] Mortality is high when children initiate ART with advanced disease, particularly in the initial weeks of treatment, with deaths predominantly caused by severe bacterial infections, pneumonia, and tuberculosis.[4] New approaches are urgently needed to reduce mortality in children presenting late, who are often diagnosed with HIV during hospitalisation for severe illness; however, few studies have been done to inform timing of ART initiation in sick, hospitalised children. Our experience is that clinicians often wait until completion of treatment for acute infections and adherence counselling sessions, due to concerns about overlapping toxicity of medications, potential for immune reconstitution inflammatory syndrome (IRIS), and poor adherence to ART. However, mortality among children waiting to start ART is high[5,6] and better evidence is needed to guide decisions about timing of treatment.

In The Lancet HIV, Irene Njuguna and colleagues[7] report the results of the Pediatric Urgent Start of HAART (PUSH) trial, which compared timing of ART initiation among HIV-infected children aged 0–12 years, hospitalised with non-CNS co-infections at four sites in Kenya. Children were randomised to urgent ART, within 48 h of enrolment, or post-stabilisation ART, started 7–14 days after enrolment. Children in this trial were young (median 1·9 years), with a high prevalence of malnutrition, tuberculosis, and pneumonia; two-thirds had WHO stage 3 or 4 disease and half had severe immunosuppression, which are all risk factors for mortality.[8] Overall, the researchers observed no differences in mortality, growth, or immune reconstitution between groups and the trial was stopped early for futility on advice of the Data and Safety Monitoring Board. Importantly, however, starting ART early during treatment for non-CNS co-infections (including tuberculosis in a third of children) had no apparent disadvantages, because no significant increases in drug toxicity, IRIS, or virological failure occurred. Of note, children in the accelerated arm started ART within 48 h of trial enrolment, but about 5 days after admission to hospital and it is tempting to speculate whether outcomes would have been improved by even earlier ART, given that 10% of the whole cohort died in the first week of the trial. However, ART could probably not realistically be started much sooner in sick hospitalised children, because of the time taken for HIV diagnosis (particularly when molecular testing is required in young children), acute stabilisation, and caregiver counselling. Overall, almost a quarter of children died by 6 months, showing the clear need for additional strategies to improve outcomes.

What does this mean for clinicians treating children in sub-Saharan Africa? WHO has produced new guidelines[9] for management of HIV-infected individuals presenting with advanced disease, which emphasise the importance of rapidly providing a package of interventions to reduce early mortality. In these recommendations, children younger than 5 years, and those older than 5 years with CD4 counts of less than 200 cells per μL or WHO stage 3 or 4 are all considered to have advanced disease and should therefore receive the package of care including screening for infections, CD4 cell counts to identify late presenters who might not be symptomatic, treatment or prophylaxis for major opportunistic infections, rapid ART initiation (within 7 days of HIV diagnosis), and intensified adherence support interventions. The PUSH trial provides reassurance to clinicians that rapid ART initiation, as recommended by these new guidelines, is safe and feasible; however, this trial also confirms that earlier ART alone is insufficient to prevent early mortality. The evidence is very limited to inform the package of care for children younger than 5 years, but at a minimum, co-trimoxazole and isoniazid prophylaxis (for those older than 1 year without current tuberculosis) should be started alongside routine interventions (deworming, malaria prophylaxis, iron and vitamin A supplementation, and growth monitoring).[9] In older children and adults, an enhanced bundle of antimicrobial prophylaxis containing co-trimoxazole, isoniazid, fluconazole, azithromycin, and albendazole reduced mortality by 27% compared with co-trimoxazole alone in the REALITY trial,[10] but this is not yet recommended in global guidelines because of concerns about cost and

potential increase in antimicrobial resistance. How such a package could be adapted for young children warrants further research.

Earlier diagnosis remains of paramount importance to prevent advanced disease. In the PUSH trial, a third of children had previously been hospitalised, showing the frequently missed opportunities for earlier HIV testing and ART initiation that have been described elsewhere.[11,12] As we sustain our efforts to eliminate mother-to-child transmission of HIV, more needs to be done to ensure that HIV services are included in the minimum package of care provided in high-burden countries, to ensure universal health coverage and ultimately improved child survival globally.

Andrew J Prendergast, Martina Penazzato
Blizard Institute, Queen Mary University of London, London E1 2AT, UK (AJP); Zvitambo Institute for Maternal and Child Health Research, Harare, Zimbabwe (AJP); Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (AJP); and HIV/AIDS Department, World Health Organization, Geneva, Switzerland (MP)
a.prendergast@qmul.ac.uk

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