

Improving treatment outcome for children with HIV



Over 2 million children are infected with HIV, and around 700 children die of HIV/AIDS-related causes every day. Almost all children with HIV infection have been infected through perinatal transmission, and without antiretroviral treatment over half will die before the age of 2 years.¹

Antiretrovirals have had a dramatic effect on the course of HIV/AIDS in children. Trials show excellent long-term outcomes with protease inhibitors and non-nucleoside reverse-transcriptase inhibitors,² and current guidelines recommend starting antiretroviral therapy in children as soon as possible after diagnosis of HIV infection.³ Poor availability of efficient antiretroviral regimens, unclear strategies for optimum drug sequencing, and maintenance of high adherence from infancy and throughout adolescence to adulthood are important challenges to long-term treatment success.⁴

In *The Lancet*, the PLATO II investigators⁵ report a cohort collaboration in Europe which assessed the risk of triple-class virological failure in children. Just over 1000 children were followed up for a median of 4.2 years. By the end of follow-up, 335 (33%) had started a drug from a third class, of whom 105 were on a failing regimen. The estimated cumulative proportion of children with triple-class virological failure was 12% at 5 years; when the analysis was restricted to children exposed to boosted protease inhibitors, the cumulative proportion was about twice that seen in adults in the same cohort collaboration (8.2% vs 4.2%). Older age when starting antiretroviral therapy (10–15 years) was associated with an increased risk of triple-class virological failure, but among all those who had such virological failure, about a quarter never achieved virological suppression; the average age of this group was less than 2 years.

Evidence from treatment programmes supports the feasibility and benefits of antiretroviral therapy, even in highly under-resourced settings,⁶ and the results from PLATO II need to be considered in context: more than a quarter of patients in the cohort had started treatment before 2000 when less potent treatments were used and treatment guidelines were poorly standardised.

Nevertheless, these data raise several concerns. Although the overall rate of triple-class virological failure was low, treatment durability is more crucial in

children than in adults. Achieving sustained virological suppression is the goal irrespective of the patient's age, and the fact that very young children might never achieve virological suppression is cause for concern. For young children, whose adherence depends on caregivers, treatment options are extremely limited and poorly adapted. Of the 22 antiretroviral drugs currently approved by the US Food and Drug Administration, five are not approved for use in children and six are not available in paediatric formulations.⁷ Additionally, treatment has to be constantly adjusted for bodyweight, and most paediatric antiretrovirals are formulated as syrups (often in large volumes) which are difficult to administer and store, while boosted protease inhibitors are extremely unpalatable. Such complications contribute to the explanation of why, in PLATO II and other studies,^{8,9} children are more prone to virological failure than are adults.

These issues are all the more important in resource-limited settings, where over 90% of children living with HIV/AIDS reside. WHO and treatment providers, such as Médecins Sans Frontières, are pressing for more widespread use of solid formulations, including fixed-dose combinations. Currently only four quality-assured triple-drug fixed-dose combinations are available in solid and dispersible forms from manufacturers of generic drugs, and less desirable dose formulations continue to dominate this small and fragmented market.¹⁰ WHO's

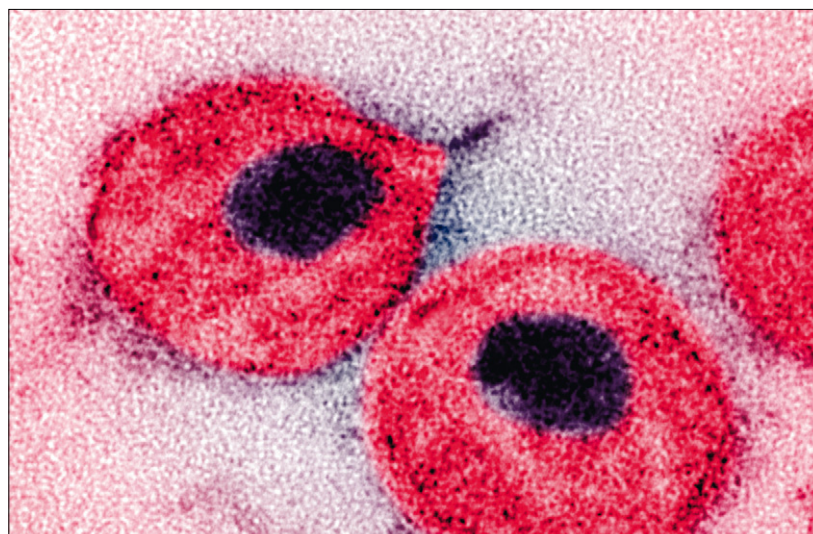
Published Online

April 20, 2011

DOI:10.1016/S0140-6736(11)60363-2

See Online/Articles

DOI:10.1016/S0140-6736(11)60208-0



Transmission electron micrograph of HIV virions

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efforts to issue user-friendly dosing tables are welcome, but the fact that newer paediatric antiretrovirals are not currently part of WHO's work on priority medicines for maternal and child health is a concern.¹¹

The development of new fixed-drug formulations is hindered by scarcity of clinical data about the use of specific drugs in children. Tenofovir has not been validated by regulatory authorities for use in patients under 12 years of age. No data about the safety of efavirenz or atazanavir in younger children are available. And new drug classes, such as CCR5 antagonists and integrase inhibitors, are not approved for use in children younger than 16 years.¹² Drug developers, clinical-trial investigators, and drug regulators all have a responsibility to prioritise the pursuit of paediatric indications for antiretroviral drugs.

The neglect of children in the global HIV/AIDS response runs from clinical research to programme implementation, with children receiving a lower standard of care than do adults. Paediatric HIV/AIDS is, for the most part, a disease of developing nations, where there are few profit prospects for drug companies. The fact that the Drugs For Neglected Diseases Initiative,¹³ a partnership originally established to develop drugs for tropical diseases, has recently included paediatric HIV/AIDS in its portfolio is telling: paediatric HIV/AIDS is a neglected disease.

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We declare that we have no conflicts of interest.

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