Does the CHER trial open up new therapeutic perspectives?

The children with HIV early antiretroviral (CHER) trial, which began participant enrolment in 2005, released interim results in 2008 showing that early antiretroviral therapy (ART) in HIV-infected infants aged 6–12 weeks reduced all-cause mortality by 76% and HIV disease progression by 75%.[1] These results prompted WHO to change their recommendations from initiation of ART in infants at a particular CD4 threshold to universal ART, irrespective of the immunological or clinical stage of disease.[2]

An earlier meta-analysis showed that without ART, 50% of HIV-infected children would be dead before they reached 2 years of age.[3] In view of this finding, and for programmatic reasons, in its 2010 guidelines WHO recommended universal ART for all children younger than 2 years.[4]

In *The Lancet*, the CHER trial team provide their final results, which show that early time-limited ART (early ART with treatment interruption at week 40 or week 96, until a particular percentage of CD4-positive T lymphocytes threshold was reached) was superior to deferred treatment.[5] The interruption was also safe in terms of disease progression, although, as the authors acknowledge, the study was not powered to detect differences between the two treatment interruption groups. Furthermore, the authors did not include a group treated with early continuous ART for comparison.

Treatment interruptions, however, require children to be closely monitored, clinically and immunologically, to ensure that disease progression is detected early and ART restarted when necessary. This approach might not be feasible in most resource-poor settings in sub-Saharan Africa, which is where more than 90% of all children with HIV live.[6]

The recently released WHO consolidated ART guidelines[7] recommend that all HIV-infected children younger than 5 years should start on ART, irrespective of their clinical or immunological stage. The CHER trial results[1,5] provide strong evidence for this recommendation in infants. However, for children aged 1–5 years, the evidence is not as strong. In fact, a clinical trial in Thailand and Cambodia indicated no benefit of starting ART early as opposed to deferring treatment until the previous WHO-recommended CD4 thresholds were reached.[8] However, this trial was not sufficiently powered to detect differences, suggesting that further research into early ART in this age group is needed.

ART coverage in children worldwide is only 28%,[6] partly because until now clinicians have been required to know the CD4 count and CD4 percentage in children aged 2–5 years in WHO clinical stages I and II before starting ART in children.[4] With the new WHO recommendation, such information is no longer needed and therefore treatment coverage is expected to improve greatly.

The CHER trial also showed the robustness of the lopinavir–ritonavir-based treatment regimen, in line with the previously reported superior virological outcome in children 2–36 months of age with this treatment compared with a nevirapine-based regimen.[9] WHO 2013 guidelines[7] recommend that all children younger than 3 years should be started on lopinavir–ritonavir-based regimens, irrespective of whether or not they have previously been exposed to perinatal prophylactic antiretroviral drugs. However, the rollout of this new strategy might be challenging for national programmes because of the supply chain and other logistical issues associated with these drug formulations.

In the CHER trial, infants started ART at a median age of 7 weeks. Even better results could be achieved if we could treat HIV-infected neonates earlier. In Mississippi, USA, a functional cure was reportedly obtained in an HIV-infected baby who received ART 31 h after birth.[10,11] The baby's caregivers decided to stop treatment at 18 months. HIV tests at 26 months found only tiny genetic traces of the virus, but the virus did not seem to have integrated into cells. The International Pediatric Adolescent Aids Clinical Trials group is planning a formal clinical trial to test the strategy of treating HIV-infected neonates with ART to obtain a functional cure. A three-drug ART regimen will be given to at-risk infants and a fourth drug will be added if a child tests positive for HIV. At 3 years of age, if there is no evidence of HIV infection in the children, ART will be stopped to see if the virus returns.[12] The recently published Visconti study[13] showed that some HIV-infected adults with primary infection who started ART very early could remain off therapy for several years without a viral load rebound.

The CHER trial, together with the Mississippi baby and the Visconti patients, opens up new therapeutic perspectives. Indeed, if we were able to diagnose HIV

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See **Articles** page 1555

infection in neonates very early and start ART shortly after birth, a prolonged period without ART, and perhaps even a functional cure in some children, can be expected.

In conclusion, early ART in infants is undoubtedly beneficial, but our knowledge about the consequences of treatment interruptions remains incomplete. Presently, such a strategy is programmatically difficult to implement in resource-poor settings because of the requirement for CD4 count monitoring. However, in the future, straightforward point-of-care tests, such as a combined RNA–DNA test,[14] will probably become available for very early infant diagnosis. Together with new methods to monitor the infection, cessation of ART after a prolonged course of a highly effective treatment regimen could become an option. Certainly, children will benefit from an improved, drug-free quality of life but we will need to be sure that this approach will not cause them any harm.

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The global burden of drug use and mental disorders


Nevada Wier/Corbis

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See **Articles** pages 1564 and 1575

Reports by Harvey Whiteford[1] and Louisa Degenhardt[2] and their respective colleagues in *The Lancet* represent the culmination of an impressive collaborative programme of research that has estimated the global burden of disease (GBD) associated with numerous risk factors[3] and diseases.[4,5] The importance of this project in guiding policy cannot be overestimated. The major findings to emerge from the present reports are that mental and substance use disorders (including alcohol and other drug use disorders) accounted for an estimated 7·4% (95% uncertainty interval 6·2–8·6) of disability-adjusted life years (DALYs) and 22·9% (18·6–27·2) of years lived with disability (YLDs) worldwide in 2010. Degenhardt and colleagues[2] report that, despite relatively low global prevalence of illicit drug use disorders, these conditions make substantial contributions to global mortality and morbidity, accounting for 0·8% (0·6–1·0) of global all-cause DALYs in 2010. Mental and substance use disorders were directly responsible for 0·5% (0·4–0·7) of years of life lost (YLLs), with more than 80% of these deaths attributable to drug use disorders. Lower estimates of YLLs (relative to estimates of DALYs) occurred because most excess deaths in individuals with a mental disorder were coded to the direct physical cause of death rather than to the disorders themselves.

In view of the severe and debilitating nature of mental and illicit drug use disorders, their contribution to the global burden of disease, and the notable economic burden associated with them, it is perhaps surprising that there has been relatively little research on the