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CHAPAS-3 fills the gap

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While the efficacy of protease inhibitors versus non-nucleoside reverse transcriptase inhibitors for first-line paediatric antiretroviral treatment (ART) has been carefully assessed in clinical trials, only one small trial (PENTA-5)[1] has compared different nucleoside reverse transcriptase inhibitor (NRTIs) backbones in children. The PENTA-5 trial noted that abacavir-containing regimens were more effective than zidovudine plus lamivudine, but was done in resource-rich settings and the regimen included nelfinavir in nearly half of participants, restricting its relevance to current treatment decision in Africa, where most paediatric HIV infections occur. Consequently, to inform its recommendations on the optimum dual NRTI backbone for paediatric ART, the WHO has relied on data from randomised trials without head-to-head comparisons of NRTIs, observational cohort data, and expert opinion. The near complete absence of trial data in children is unacceptable in the context of lifelong ART, which requires a good understanding of the effect of different NRTI backbones on toxicity, achievement and maintenance of viral suppression, and implications of mutations on future treatment options. The CHAPAS-3 trial[2] now fills this gap by providing the first trial data comparing abacavir, stavudine, and zidovudine in combination with lamivudine and nevirapine or efavirenz for first-line treatment in HIV-positive children in Africa.

In 2013, the WHO recommended abacavir plus lamivudine as the preferred dual NRTI backbone in children because "abacavir can be used once daily, is available as a fixed-dose combination with 3TC [[lamivudine], and harmonises with TDF [tenofovir] from a resistance perspective".[3] This change occurred despite the relatively high cost of abacavir and the association of abacavir with hypersensitivity reactions.[4] Furthermore, observational data from two cohort studies indicated that abacavir might be less effective in achieving and maintaining viral suppression compared with similar regimens containing stavudine, raising concerns among clinicians and policy makers about the WHO recommendation.[5,6]

In the multicentre CHAPAS-3 trial,[2] 478 children age 1 month to 13 years were randomly assigned to receive fixed-dose combination tablets of one of three NRTIs (abacavir, stavudine, or zidovudine) plus lamivudine in combination with nevirapine or efavirenz, all dosed according to WHO weight bands. The trial included 365 ART-naive children and 113 virologically suppressed ART-experienced children on a stavudine-containing first-line regimen for 2 years or more. The study achieved superb completion rates with only 5% of children lost to follow-up and 98% of scheduled nurse visits completed. Clinical outcomes

were excellent for all three NRTIs, with low (4%) mortality, high (≥80%) viral load suppression rates in ART-naive children, high (>96%) maintenance of viral suppression at 48 weeks in ART-experienced children, and no evidence of differential CD4% recovery across randomised groups.

In children with ongoing viral replication, sensitivity to second-line drugs remained high independent of the NRTI used. Toxicity was low and independent of NRTI group, with no differences noted in the proportion of children with grade 2 or more clinical or grade 3 or more laboratory adverse events (67% in stavudine group, 65% in zidovudine group, and 64% in abacavir group; p=0·63) with grade 2 respiratory tract infections accounting for more than half of all primary endpoints. Few children (4% who received stavudine, 8% who received zidovudine, and 3% who received abacavir) presented with grade 3 or more adverse events with possible relations to NRTIs, and only 6% of children changed regimens during the 2·3 years of median follow-up. Of note, a higher proportion of children in the zidovudine group then in the other two treatment groups had their ART regimen modified as a result of toxicity, even though there was no evidence that grade 3 or 4 anaemia was more frequent in that group. This finding potentially indicates a lower threshold among clinicians to modifying therapy in children receiving zidovudine. The endpoint review committee diagnosed nine children with a hypersensitivity reaction: five in the stavudine group, one child on zidovudine, and two receiving abacavir (p=0·21). Both children receiving abacavir continued the drug without adverse consequences, a finding that shows the difficulty in making an accurate clinical diagnosis of abacavir hypersensitivity.

In conclusion, the CHAPAS-3 trial[2] refutes the concerns of reduced efficacy of abacavir-containing NRTI backbone for first-line ART that was raised by observational studies, and strongly suggests that NRTI backbone with efavirenz or nevirapine in children is associated with very low toxicities and high viral load suppression rates independent of the NRTI used. These data are reassuring and support clinicians and policy makers in their implementation of the current WHO guidelines, which recommend abacavir plus lamivudine as the preferred NRTI backbone for paediatric ART.

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Artemisinin-based combination therapy for knowlesi malaria

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For decades, human *Plasmodium knowlesi* infections were misclassified as other forms of human malaria because of their morphological similarities seen during microscopic assessment.[1] This misclassification became evident only with the availability of molecular diagnostic techniques. Since then, results of intensive research have shown that *P knowlesi* infection can progress rapidly to severe disease in the human host as a result of its 24 h asexual reproduction cycle, that *P knowlesi* is the most prevalent human malaria species in Malaysia, and that other countries in southeast Asia also harbour substantial numbers of human cases of this simian malaria parasite.[2,3] Importantly, there is no evidence for a direct transmission cycle between human beings and the anopheline vector; monkeys are the necessary intermediate host sustaining ongoing transmission of this zoonotic *Plasmodium* species.[3]