Response of HIV-1-Infected Children in Kenya to Antiretroviral Therapy

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HIV-1-infected children need to continue receiving combination antiretroviral therapy (cART) into adulthood. This places great importance on understanding the long-term successes and failures of different treatment options, as well as the evolution of drug resistance over protracted periods of therapy. The majority of the world's two million HIV-1-infected children reside in Africa, where options for cART are often limited. Very little is known about either the outcomes of cART in African pediatric cohorts for periods exceeding one year, or the patterns of resistance mutations that arise in this setting. In a recent collaboration between the University of Nairobi and the Fred Hutchinson Cancer Research Center, scientists describe first-line and second-line treatment outcomes and patterns of drug resistance that have arisen in a cohort of HIV-1-infected children in Kenya.

Countries around the world have established different standardized lines of treatment for HIV disease, which are tailored to be safe, available and effective for the greatest number of citizens. First-line cART is the preferred initial therapy for individuals that have not been treated previously with antiretroviral drugs against HIV-1. However, resistance to multiple classes of antiretroviral drugs can arise owing to the short replication cycle of HIV-1 and the virus's propensity for mutating its genome. Thus, second and subsequent lines of therapy have also been established to deal with this problem of drug resistance. All levels of therapy may be modified as new antiretroviral drugs become available. In many African settings, resource limitations restrict cARTs to the first- and second-line regimens that can be reliably provided to infected individuals locally. In addition, because it is often not practical to routinely measure viral loads in these settings, the standard of care for switching treatment regimens may be limited to immunological (e.g., CD4 cell count) and clinical criteria. However, clinical and immunological measures alone may not always detect failing cART regimens, and continued treatment with failing regimens can hasten the emergence of multi-class drug resistant HIV-1 strains.

Dr. Dalton Wamalwa (Department of Pediatrics, University of Nairobi) and Dr. Dara Lehman (Human Biology Division, Fred Hutchinson Cancer Research Center) co-led a long-term study of HIV-1 responses and drug resistance mutations in Kenyan children. Dr. Julie Overbaugh (Human Biology Division) was also a major contributor to the study. These three researchers and their collaborators investigated a cohort of 100 children between the ages of 18 months and 12 years, who were started

on first-line cART at the Kenyatta National Hospital (Nairobi, Kenya) and were and followed for up to 5.5 years. First-line therapy consisted of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse-transcriptase inhibitor (NNRTI). Following current guidelines set by the Kenya Ministry of Health, some children were switched to second-line cART (a protease inhibitor plus two new NRTIs), based on clinical and/or immunological criteria. Throughout the study, Wamalwa *et al.* measured CD4 cell counts in the children and sent frozen plasma samples to the Hutchinson Center for retrospective viral load measurements. In children with 'virologic failure' (*i.e.*, two or more blood samples with viral loads exceeding 5,000 copies of HIV-1 RNA per milliliter of plasma), the investigators also genetically screened a region of the HIV-1 *pol* gene for drug resistance mutations.

The authors found that virus levels were successfully suppressed in 66 of the 100 children on first-line cART. The remaining 34 children exhibited virologic failure a median of 9 months after starting first-line therapy. Children less then 3 years old when first-line cART was initiated were significantly more likely to experience virologic failure. Wamalwa *et al.* also found that in 23 of the 34 children with virologic failure, detectable levels of drug-resistant HIV-1 had evolved prior to virologic failure. A majority of these children had multi-class resistance HIV-1. Based on clinical or immunological criteria, fourteen of 100 children in the cohort were switched to second-line cART a median of 30 months after initiation of first-line therapy. However, the researchers retrospectively found that twelve of these children had exhibited virologic failure a median of one year prior to the switch to second-line therapy. These children could have been switched to second-line treatment earlier if viral monitoring had been available to them. Instead, they received extended first-line treatment in the presence of unrecognized virologic failure. Similarly, 22 children had not been switched to second line-line treatment during follow-up care, though Wamalwa *et al.* found retrospective evidence that they exhibited unrecognized virologic failure on first-line treatment. The researchers documented several instances in which these children acquired single-class or multi-class resistance during this extended period of first-line cART. Sixty-two percent of the children who were switched to second-line cART showed consistent virologic suppression on the new regimen, while only 7% exhibited persistent viremia during a median follow-up period of 28 months on second-line therapy.

Some of these results are encouraging about the outcome of cART in resource-limited regions of the world. However, the findings also highlight important pitfalls in the standard of care for pediatric HIV-1 in these settings. On the one hand, two-thirds of children showed viral suppression for up to four years on first-line cART, and most of the children who were switched to second-line treatment exhibited excellent viral suppression on the new regimen despite a lag of about one year between virologic failure and the new treatment. On the other hand, the authors also demonstrated that the delay until second-line treatment could be lessened by viral load assays, thereby reducing the

accumulation of HIV-1 resistance mutations. Resistance assays would also help medical investigators distinguish cases of virologic failure caused by drug resistance from cases of virologic failure due to non-adherence to a prescribed cART regimen. When and where the resources for such tests are available, the authors recommend that priority should be given to the youngest HIV-1-infected children.

Wamalwa D, Lehman DA, Benki-Nugent S, Gasper M, Gichohi R, Maleche-Obimbo E, Farquhar C, John-Stewart G, Overbaugh J. 2013. Long-term virologic response and genotypic resistance mutations in HIV-1 infected Kenyan children on combination antiretroviral therapy. *J. Acquir. Immune Defic. Syndr.*, Epub ahead of print, doi: 10.1097/QAI.0b013e31827b4ac8.

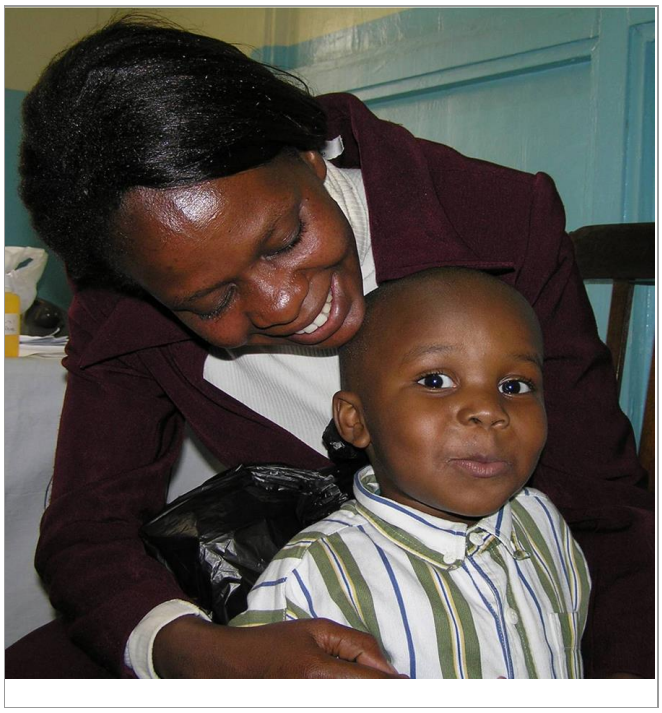

Photo by Dalton Wamalwa, MBChB, MMed, MPH.

One of the study participants with his mother in the Pediatrics Ward of the Kenyatta National Hospital (Nairobi, Kenya), photographed with the mother's permission.