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Raltegravir: a new choice in HIV and new chances for research

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In *The Lancet* today, Jeffrey Lennox and colleagues (the STARTMRK investigators) present important information about the efficacy of the latest antiretroviral drug for HIV infection, raltegravir.¹ Raltegravir is the first drug in a new class designed to retard HIV replication through inhibition of the virus-encoded enzyme that integrates viral genes into the DNA of the host cell—an HIV integrase inhibitor.^{2,3}

For the past 10 years, development of antiretrovirals for HIV infection has been brisk. The number of licensed drugs has more than doubled to 26. Drugs now inhibit HIV replication at five different viral targets. As a direct consequence of this increasing sophistication in therapeutic weaponry, coupled with improved understanding of how these drugs should be used, extraordinary improvements in prognosis for patients with HIV infection have been achieved. A person who starts combination antiretroviral treatment (cART) at 20 years of age is estimated to live for a further 30 years, which is an improvement of about 13 years compared with life expectancy for 1996–99.⁴ Despite the progress, life expectancy for people with HIV is lower than that of the general population, perhaps by as much as a third. If we assume much of this excess mortality arises from inadequate cART, the continued development of new

drugs is crucial to improve outcomes. New drug discovery is also important to promote critical thinking about HIV and further research.

Raltegravir is already licensed for treatment of HIV infection in patients with evidence of refractory responses to other drug classes because it had extraordinary potency in two randomised trials.^{5,6} Paradoxically, we also know that treatment with raltegravir can be fragile. Results from as yet unpublished trials, in which raltegravir was substituted for an HIV protease inhibitor, showed that substitution was inferior for suppression of HIV replication.⁷ The inferiority of raltegravir was perhaps due to episodes of treatment failure preceding the study, which were caused by HIV drug resistance in at least some patients. Switching to raltegravir amounted to antiretroviral monotherapy with rapid selection of raltegravir-resistant HIV.

Lennox and colleagues' study compared the efficacy of raltegravir and efavirenz, with each drug in combination with tenofovir and emtricitabine, in adults with HIV infection who were naive to antiretroviral therapy. Raltegravir suppressed HIV replication far more rapidly than efavirenz, confirming reports from previous studies, but the relevance of such rapid viral decay remains unclear.⁸ At 48 weeks, the proportions of patients with

plasma HIV RNA concentration below the limits of assay detection indicated that raltegravir was non-inferior to efavirenz. Raltegravir is a viable alternative to efavirenz for initial therapy on the basis of potency and sustained suppression of HIV replication.

Raltegravir seems to have an edge over efavirenz in terms of safety and tolerability. Patients treated with raltegravir had significantly fewer clinical adverse events, including those judged to be drug-related. Significantly fewer CNS side-effects and smaller perturbations in serum lipid concentrations were recorded in patients on raltegravir than in those on efavirenz. More patients discontinued the trial because of drug-related adverse events in the efavirenz group than in the raltegravir group. This finding is robust because the trial was blinded for the efavirenz and raltegravir components of the regimens. A potential limitation with raltegravir is the requirement for twice daily dosing that could add complexity when administering compact combination regimens in some patients. The results of studies that are assessing once daily dosing with raltegravir are eagerly anticipated, as are developments in formulation chemistry to create fixed-dose combinations that include HIV integrase inhibitors.⁹

On the assumption that raltegravir is recommended for use in first-line combination therapy, how might use of this drug affect future treatment regimens? First, we now have more choice to offer patients beginning their first treatment regimen, which is especially important for women of child-bearing potential because choosing to begin treatment is no longer limited by concerns about the teratogenicity of efavirenz. Second, raltegravir seems to be free from clinically relevant drug–drug interactions, although results of a study in which raltegravir was co-administered with rifampicin indicate that continued vigilance is warranted in individuals co-infected with tuberculosis and HIV.¹⁰ Third, integrase inhibitors are not likely to be vulnerable to transmitted HIV drug resistance. And fourth, a new drug class should increase the number of plausible regimens that could be used during an individual's lifetime.

In view of the availability of this potent and well-tolerated new antiretroviral drug, perhaps the time has been reached to break away from the dogma of cART regimens being based on two nucleos(t)ide analogue reverse-transcriptase inhibitors [N(t)RTIs] and a third drug. Surely the long-term benefits of creative combinations are worth exploring, such as an integrase



Krista Kennell/ZUMA/Corbis

inhibitor (eg, raltegravir) combined with a boosted protease inhibitor. N(t)RTIs might be more effective if kept for a later stage in treatment algorithms. Cohort studies are essential both to estimate the additional benefit of new drugs, and to detect low-frequency adverse outcomes. Raltegravir looks remarkably safe and well tolerated but the total exposure time at present is short. Unfortunately up to now, adverse side-effects and unfavourable drug–drug interactions have unerringly constrained progress with every antiretroviral drug class.

However, today's data are very encouraging for treatment and research. Raltegravir is an impressive drug and we hope other integrase inhibitors in development offer similar benefits.

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Children’s mental health in Afghanistan

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In *The Lancet* today, Catherine Panter-Brick and colleagues report a school-based survey about violence and mental health in Afghanistan.¹ They make the first substantial contribution about the scope and impact of political conflict and other traumatic events on 11–16-year-old Afghan children. The findings confirm cross-cultural similarity in mental health outcomes in children in adverse circumstances and some of the factors that have a protective role.^{2,3} Support is also provided for the risk-accumulation model of Garbarino and Kostelny,⁴ in which mental health problems in children escalate substantially when the children are exposed to more than five traumatic events. Of particular interest is the finding that traumas that were not related to war were among those most distressing to children. The implication for mental health interventions is that a narrow focus on conflict-related trauma as the source of all psychological distress observed in war-affected children might not be appropriate. The study therefore draws attention to the need for a broader understanding of the multiple sources of children’s

distress in both conflict and postconflict situations, and the need for holistic culturally appropriate responses.

Schools are recognised as potentially (though not necessarily) protective environments for children living in areas affected by conflict.^{5,6} Panter-Brick and colleagues draw attention to the potential of schools as sites for intervention to address children’s mental health. School-based programmes have been started in Afghanistan as part of a holistic response to communities affected by the conflict. For example, Kostelny reports on an initiative that trains teachers to recognise and provide basic psychological support to war-affected children.⁶ Because schools themselves are often sites of exposure to violence, the programme has engaged education officials in an effort to reduce (commonly used) harsh physical punishment. No evaluations of these initiatives are yet available.

Although school-based interventions are often appropriate, they can be undermined by challenges in the education system. In Afghanistan, as Panter-Brick and colleagues point out, the educational system is under considerable strain. One has to question whether in these circumstances teachers are likely to have the time and emotional resources to support children in distress. It is for this reason that programmes described by Kostelny and others seek to strengthen the functioning of educational systems alongside provision of psychological support to children.^{6,7}

Experience in Afghanistan points to the importance of giving children opportunities to present their concerns when designing interventions to improve their wellbeing. Consulting children and young people is particularly difficult in a patriarchal society and, to overcome this barrier, innovative methods for participation by children have been devised.⁷ In one large programme, adolescents are assisted to gather information on risks to their

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