

Generic antiretroviral drugs—will they be the answer to HIV in the developing world?

Christian Laurent and colleagues, in today's *Lancet*, report on the efficacy and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon. Highly active antiretroviral therapy (HAART) has led to dramatic reductions in HIV-related morbidity and mortality in the USA and in India.^{1,2} The use of HAART has led to cost-effective public-health programmes in countries such as Brazil, because there are now fewer episodes of illness and hospital admission.³ The cost of combination HIV-antiretroviral treatment has plummeted in the past 12 months, such that HAART can now be bought for less than US\$250 a year from Cipla and other generic companies. Cipla is a drug company in Mumbai, India, that launched the first generic antiretroviral drug, zidovudine, in 1994 (figure). Since then, Cipla has launched ten different antiretroviral and fixed-dose combinations of antiretroviral drugs as single pills. Falling prices of therapy are enabling physicians in the developing world to offer triple antiretroviral regimens to greater numbers of patients, who desperately need the life-saving drugs. The safety, tolerability, and efficacy of generic antiretroviral regimens for HIV-infected Indians has been shown.⁴ Also there were earlier reports that generic antiretroviral drugs were successfully used in HIV-infected patients in Africa.⁵

The bioequivalency of the generic drugs is equivalent to proprietary drugs.⁶ Most of the studies and reports used CD4 cell-counts and clinical markers to assess the efficacy of generic antiretroviral treatment.^{4,5} Laurent and colleagues used HIV-RNA to measure efficacy in African patients and found viral suppression with the generic regimen. These investigators recruited 60 patients in an open-label one-arm 24-week trial. All patients received, twice daily, one tablet of Triomune, which is a fixed-dose combination of stavudine, lamivudine, and nevirapine. The primary endpoint of the study, the proportion of patients with HIV-RNA below 400 copies per mL at 24 weeks was achieved in 80%. The probability of remaining alive or free of new AIDS-defining events was 0.85. Incident rates of disease progression, severe adverse effects, and genotypic resistance-mutations were, respectively, 32.0, 17.8, and 7.1 per 100 person-years. Mean adherence rate was 99%. Median nevirapine,

stavudine, and lamivudine concentrations in tablets were 96%, 89%, and 99% of expected values, respectively. See [Articles](#) page 29

Similar reductions in viral load with generic drugs made by Cipla were seen in a clinical trial in southern India.⁷ On the basis of these reports there is no question about safety and efficacy of generic antiretrovirals. Generic antiretrovirals will have a major role in WHO's scaling-up of antiretroviral delivery in their 3-by-5 plan in resource-constrained settings. Because of patents by proprietary companies, newer antiretrovirals may not be manufactured by the generic companies, which might be a major obstacle to patients getting drugs in such settings.

Adherence to these antiretroviral drugs is crucial to suppress virus levels and prevent resistance.⁸ In clinical settings, maintaining absolute adherence is a monumental task. In resource-constrained settings, where many patients buy antiretrovirals from a pharmacy because such drugs are not available in government programmes, such patients might stop taking their drugs when they can no longer afford them, which could lead to the emergence of multidrug-resistant HIV. Directly-observed HIV therapy is the key to success.⁹

The cost of first-line combination generic antiretrovirals is less than \$250 a year. But the cost of the second-line combinations with protease inhibitors is ten times that amount. This large disparity in price will present a great challenge in resource-constrained settings in the scaling-up of antiretroviral delivery. Maintaining the cold chain to store protease inhibitors will also be a challenge in such settings where refrigerators are not available or which suffer power cuts with no backup.

Immunological and virological monitoring of HIV-infected patients on HAART are critical. The cost of a CD4 cell-count is around \$25 a test, and measuring viral load costs \$100 a test. The cost of monitoring is higher than the cost of generic antiretrovirals. Mixed results were seen in studies which evaluated usefulness of low-cost total lymphocyte counts in first assessment and monitoring of HIV-infected patients for HAART.^{10,11} Thus there is an urgent need to evaluate cost-effective simple techniques to measure CD4 cell-count^{12,13} and HIV-RNA.^{14,15}

In developing countries, patients who need antiretrovirals often have multiple opportunistic and concomitant infections.² There are several interactions between drugs for opportunistic infections and antiretrovirals including those leading to varying serum concentrations of drugs.¹⁶ Some interactions such as hepatitis, may be fatal, especially those between protease inhibitors and drugs for tuberculosis.¹⁷

Starting, monitoring, and managing the toxicities of antiretroviral drugs is an art and needs tremendous experience and dedication. Physicians need to be trained properly before we scale-up antiretroviral programmes. We need to emphasise that physicians should adhere strictly to standard treatment guidelines to avoid antiretroviral failure and resistance which will be a future public-health challenge in the presence of increasing use of generic antiretroviral drugs.



Figure: Cipla's headquarters in Mumbai, India

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Concurrent sexual partnerships help to explain Africa's high HIV prevalence: implications for prevention

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As Kiat Ruxrungtham and colleagues describe in today's *Lancet*, HIV transmission in most Asian countries remains strongly associated with particularly high-risk activities—ie, injection-drug use, male-male sex, prostitution and, in China, paid donation of plasma. Although there is understandable concern that the virus could soon spread widely through the general population,^{1,2} HIV has been present in Asia for nearly two decades and such extensive spread has yet to occur. For example, analysis of trends in India suggests that HIV prevalence, both in high-risk groups and in the generally low-risk antenatal clinic population, has probably stabilised in recent years.³ It is possible that large-scale heterosexual epidemics will never emerge in most of Asia, except perhaps on the island of Papua.^{4–6} Furthermore, in some of the world's most populated countries—Pakistan, Bangladesh, Indonesia, and the Philippines, home to some one billion people—nearly all men are circumcised, further restricting the potential for extensive heterosexual spread.^{7,8}

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In chilling contrast, as Emil Asamoah-Odei and colleagues report, also in today's *Lancet*, HIV rates remain very high in much of east and especially southern Africa. The overwhelming burden of HIV/AIDS is still concentrated in this region, which accounts for only 3% of the global population yet some 50% of global HIV cases.¹ For example, infection rates in adults in South Africa, Botswana, Zimbabwe, and western Kenya range from 20 to 40%, roughly an order of magnitude higher than anywhere else in the world.

What might account for this pervasive discrepancy? The strong association between lack of male circumcision and HIV risk^{9–10} helps explain the 4–5-fold difference in HIV rates between southern and western Africa discussed by Asamoah-Odei and colleagues. However, that association does not explain why HIV has spread so much more extensively in southern Africa than in India, or in Europe, where circumcision is similarly uncommon. Although sexual cultures do vary from region to region,¹¹ the differences are not so obvious. Demographic surveys and other studies suggest that, on average, African men typically do not have more sexual partners than men elsewhere. For example, a comparative study of sexual behaviour found that men in Thailand and Rio de Janeiro were more likely to report five or more casual sexual partners in the previous year than were men in Tanzania, Kenya, Lesotho, or Lusaka, Zambia. And very few women in any of these countries reported five or more partners a year.¹² Men and women in Africa report roughly similar, if not fewer, numbers of lifetime partners than do heterosexuals in many western countries.^{13–15} Of increasing interest to epidemiologists is the observation that in Africa men and women often have more than one—typically two or perhaps three—concurrent partnerships that can overlap for months or years (figure). This pattern differs from that of the serial monogamy more common in the west, or the one-off casual and commercial sexual encounters that occur everywhere.