hyperlipidemia. Nevertheless, the determination that this nonpeptidomimetic PI does not contribute to altered glucose disposal offers continued hope that additional PI-containing antiretroviral regimens that do not acutely block glucose transport can be identified. These efforts should be aided by the development of PIs that do not require ritonavir boosting. Continued use of this healthy rodent model system to assess the ability of new drugs to induce insulin resistance directly can allow efficient screening of candidate compounds before the initiation of large and expensive clinical trials.

Paul W. Hruz, MD, PhD
Departments of Pediatrics and
Cell Biology and Physiology
Washington University School of Medicine
St. Louis, MO
Qingyun Yan, MD
Department of Pediatrics
Washington University School of Medicine
St. Louis, MO

REFERENCES

1. Mulligan K, Grunfeld C, Tai VW, et al. Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. *J Acquir Immune Defic Syndr*. 2000;23:35–43.
2. Murata H, Hruz P, Mueckler M. Indinavir inhibits the glucose transporter isoform Glut4 at physiologic concentrations. *AIDS*. 2002;16: 859–863.
3. Noor MA, Seneviratne T, Aweeka FT, et al. Indinavir acutely inhibits insulin-stimulated glucose disposal in humans: a randomized, placebo-controlled study. *AIDS*. 2002;16(Suppl): F1–F8.
4. Yan Q, Hruz PW. Direct comparison of the acute in vivo effects of HIV protease inhibitors on peripheral glucose disposal. *J Acquir Immune Defic Syndr*. 2005;40:398–403.
5. Noor MA, Parker RA, O'Mara E, et al. The effects of HIV protease inhibitors atazanavir and lopinavir/ritonavir on insulin sensitivity in HIV-seronegative healthy adults. *AIDS*. 2004; 18:2137–2144.
6. Hertel J, Struthers H, Baird Horj C, et al. A structural basis for the acute effects of HIV protease inhibitors on GLUT4 intrinsic activity. *J Biol Chem*. 2004;279:55147–55152.
7. Physicians' Desk Reference. 60th ed. Montvale, NJ: Thompson PDR; 2006.
8. Hruz P, Murata H, Qiu H, et al. Indinavir induces acute and reversible peripheral insulin resistance in rats. *Diabetes*. 2002;51:937–942.
9. Foisy ML, Sommadossi JP. Rapid quantification of indinavir in human plasma by high-performance liquid chromatography with ultraviolet detection. *J Chromatogr B Biomed Appl*. 1999;721:239–247.

Scaling-Up Highly Active Antiretroviral Therapy (HAART) in Peru: Problems on the Horizon

To the Editor:

The AIDS epidemic has overwhelmed the fragile health system of developing countries. Peru is not the exception to this situation, although the HIV prevalence in the general population is still less than 1%.[1] In May 2004, the National Program, supported by the Ministry of Health and the Global Fund to Fight AIDS, Tuberculosis, and Malaria started to provide highly active antiretroviral therapy (HAART) free of charge.[2] The National Program operates as a 4-step pyramid: the Ministry of Health on top, the district health authorities and the HIV/AIDS centers at the hospitals in the middle, and the community health centers at the base.

Our hospital cares for 18% of the HIV patients under the National Program, diagnoses 400 new HIV cases, and provides 5000 HIV-related outpatient visits per year. The HIV/AIDS center at our hospital is staffed with 8 physicians. In addition, there are 2 nurses, 1 psychologist, and 1 social worker who are responsible for home visits, psychological evaluation and counseling of candidate patients, data recording, reporting adverse events, and drug dispensing. By June 2006, 716 HIV patients began HAART at our hospital through the National Program. This was achieved due to the extreme dedication of the personnel involved. But currently, our attendance capacity has been surpassed because the staff has remained constant despite the increasing number of patients undergoing follow-up. As a result, the time devoted to patient care has decreased.

The process of drug distribution currently involves many intermediate steps, which are not always successfully coordinated. As a result, there is a significant delay to obtain new drug supplies. Under these conditions, it has not been possible to enroll patients at the expected rate of 50 new patients per month (Fig. 1). In addition, CD4 cell count and viral load measurements are limited, as only 1 central laboratory is in charge of sample taking and processing for all patients from the capital Lima. Only 50% of our patients have viral load and CD4 results.

These barriers may reduce the efficacy of the program of antiretroviral therapy in our country, a concern that has been expressed also in other countries where HAART was recently introduced.[3] Increase in manpower or redistribution of health care personnel from community health centers is necessary to fulfill the increased demand of antiretroviral treatment. A decentralized, single-step drug distribution process, in which each HIV/AIDS treatment center connects

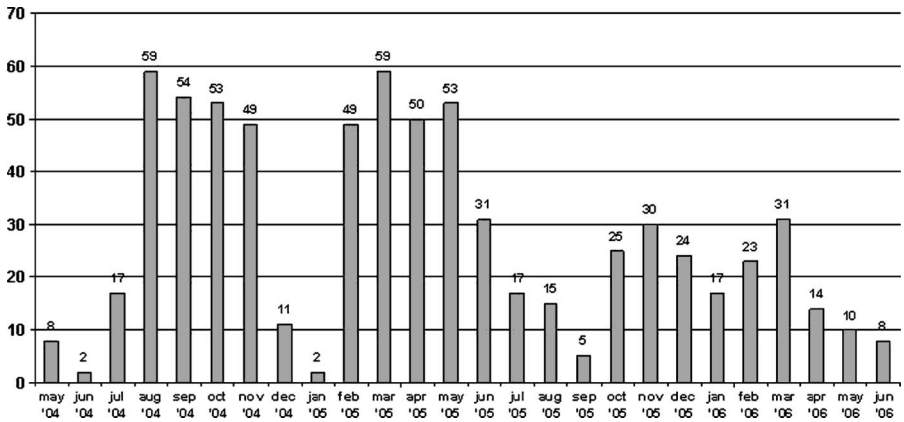

FIGURE 1. A non-continuous delivery of antiretroviral drugs supply caused a delay in initiation of HAART therapy within the National Program at 2 specific time points: between December 2004–January 2005 and between July 2005–September 2005. The numbers of the *y* axis represent the absolute number of patients.

© 2006 Lippincott Williams & Wilkins

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

directly with the district health authorities could ensure efficient drug supply. Collecting blood samples at peripheral centers and sending them to the central laboratory for processing could assure higher rates of laboratory monitoring.

Juan Echevarría*†
Diego Lòpez de Castilla†
Carlos Seas*†
Kristien Verdonck†‡
Eduardo Gotuzzo*†
*Departamento de Enfermedades Infecciosas Tropicales y Dermatològicas
Hospital Nacional Cayetano Heredia
Lima, Perú
†Instituto de Medicina Tropical Alexander von Humboldt
Universidad Peruana Cayetano Heredia
Lima, Perú
‡HIV and Retrovirology Research Unit
Department of Microbiology
Institute of Tropical Medicine
Antwerp, Belgium

REFERENCES

1. Informe sobre la epidemia mundial del SIDA. 2004. ONUSIDA Panorama Mundial de la Epidemia del SIDA. Peru. Available at: http://www.unaids.org/en/Regions_Countries/Countries/peru.asp. Accessed July 12, 2006.
2. Peruvian proposal to the Global fund to fight AIDS tuberculosis and malaria. 2002 Sep. SA.DVMN°677-2002. Available at: http://www.theglobalfund.org/programs/countrysite.aspx?countryid=PER&lang Accessed July 12, 2006.
3. Severe P, Leger P, Charles M, et al. Antiretroviral therapy in a thousand patients with AIDS in Haiti. *N Engl J Med*. 2005;353:2325–2334.

Renal Function in Patients Receiving Tenofovir With Ritonavir/Lopinavir or Ritonavir/Atazanavir in the HIV Outpatient Study (HOPS) Cohort

To the Editor:

Use of tenofovir (TDF)-containing HAART regimens has been associated with modest but statistically significant decrements in creatinine clearance in observational cohort studies[1,2] and with rare severe renal dysfunction in multiple case series,[3] but has not been associated with incident renal insufficiency in large randomized clinical trials.[4–7] Pharmacokinetic studies have shown that TDF exposure is increased when it is coadministered with ritonavir/lopinavir (rtv/LPV) or atazanavir (ATZ)[8] raising the concern for increased nephrotoxicity.[9] We sought to assess the impact of concurrent use of TDF with rtv/LPV or rtv/ATZ on renal function in HIV-infected patients with normal baseline renal parameters.

We studied patients enrolled in the HIV Outpatient Study (HOPS), an ongoing prospective cohort study that has been continuously enrolling patients in 8 cities in the United States since 1993. We compared renal function in patients receiving TDF with concurrent rtv/LPV or rtv/ATZ ("exposed") with patients receiving TDF-containing HAART without these agents or other protease inhibitors (PIs) ("unexposed"). Analyses included exposed and unexposed patients, both antiretroviral-naive and experienced, who initiated HAART regimens between November 1, 2001 and November 1, 2004, and who had serum creatinine measured at baseline (ie, closest within 12 months before starting HAART regimen of interest; median = 17 days, interquartile range; 0–49 days), and again after 12 months ($\pm$3 months) of follow-up while remaining in the same exposure category. We excluded patients who had baseline serum creatinine >1.5 mg/dL or creatinine clearance (CrCl) <50 mL/min, any history of renal disease, any prior or concurrent exposure to cidofovir or adefovir, or concurrent pregnancy. We thus assessed within-patient changes in CrCl and glomerular filtration rate (GFR) among 99 exposed (80 receiving rtv/LPV, 19 receiving rtv/ATZ) and 210 unexposed patients who had both baseline and 12-month follow-up data.

Creatinine clearance was estimated by Cockcroft-Gault equation (CG) using age and weight data closest in time to serum creatinine measurement ($\pm$3 months),[10] and GFR was estimated by simplified Modification of Diet in Renal Disease Study (MDRD) equation.[11] Baseline CD4+ cell count and HIV viral load were those obtained closest to start date of HAART regimen of interest (−12 months to +1 months). Nephrotoxic drug use history included any prior use of aminoglycoside antibiotics (except for ophthalmological use), cisplatin, foscarnet, or intravenous pentamidine or amphotecerin B. We used Wilcoxon rank sum test for comparing distributions of continuous variables, and χ^2 or Fisher exact test for categorical variables.

The exposed and unexposed groups were comparable by gender (88% vs. 85% male) and age (median = 43 years for both), but the exposed group had fewer whites (65% vs. 78%), fewer antiretroviral-naive persons (1% vs. 13%), lower baseline CD4+ cell counts (median = 352 vs. 427 cells/mm^3), higher baseline HIV viral loads (median = 3.6 vs. 2.5 copies/mL), and had been diagnosed with HIV for a longer time (median = 10.4 vs. 8.6 years), all $P < 0.05$. The exposed and unexposed patients were comparable by history of hypertension (23% vs. 15%), history of diabetes (6% vs. 4%), and history of nephrotoxic drug use (3% vs. 1%), all $P > 0.10$. The two groups also had similar baseline serum creatinine (median = 0.9 vs. 0.9 mg/dL, $P = 0.21$) and baseline CrCl by CG (median = 106 vs. 106 mL/min, $P = 0.56$) but the

This work was funded by Contract 200-2001-00133—Centers for Disease Control and Prevention.

The investigation adhered to the guidelines of the U.S. Department of Health and Human Services regarding protection of human subjects. The study protocol was approved and renewed annually by each participating institution's ethical review board. All study participants provided written, informed consent.

Disclaimer: The findings and conclusions from this review are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Conflicts of Interest: Ben Young is a consultant to Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb Company, Gilead Sciences, GlaxoSmithKline, Merck & Co., Roche, Monogram Bioscience, and is a member of the speakers' bureaus for Gilead Sciences, Bristol-Myers Squibb, GlaxoSmithKline, Monogram Bioscience, and Vertex Pharmaceuticals. Ben Young has received research funding from Agouron Pharmaceuticals, Bristol-Myers Squibb Company, Gilead Sciences, GlaxoSmithKline, Merck & Co., and Roche. Rose Baker and Kathy Wood are employees of Cerner Corporation, which has performed consulting services on behalf of Gilead Sciences. The other authors have no conflicts.

© 2006 Lippincott Williams & Wilkins

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.