



Antiretroviral Drug Content in Products from Developing Countries

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ABSTRACT

Background: Generic and discounted brand name antiretroviral (ARV) medications are becoming increasingly available in developing countries. To date, little information is available on drug content versus label claims for these medications. The purpose of this study was to assess drug content compared to the labeled amount among ARVs obtained from developing countries.

Methods: We analyzed 6 ARV medications from 6 manufacturers and 4 international sources (Lithuania, South Africa, Jamaica, and Zambia). In total, 12 different lots of medication were obtained in hospital or commercial clinic pharmacies and brought to the US unrefrigerated. Drugs were then assessed for active ingredient. Drug manufacturers included BMS (efavirenz, 1 lot), Merck (efavirenz, 1 lot; indinavir, 3 lots), Aurobindo Pharma Ltd. (indinavir, 1 lot), Abbott (lopinavir-ritonavir, 1 lot; ritonavir, 2 lots), GSK (amprenavir, 1 lot), and Roche (saquinavir soft gel caps, 2 lots). Drug content was determined with HPLC; a modified United States Pharmacopeia (USP) Uniformity of Dosage Units test was applied; this test specifies that the drug content of an individual capsule be within 85-115% of the label claim. For all analyses, 2-4 capsules were assayed 6-9 times per dosage unit. Drug content (percent of label claim) and coefficient of variation (%CV) are reported.

Results: With the exception of ritonavir, which was not stored under continual refrigeration, the active ingredient in each of the drug products was within USP specifications; drug content was between 88 and 115% of labeled amounts. The absolute value of the mean difference between measured and labeled drug content was 7.7% and the median difference was -2.0%. Amprenavir, from a single international source, was tested after its expiration date and contained 92% of its labeled amount. Ritonavir content, by itself and combined with lopinavir, was between 81 and 84% of the labeled amount in tested preparations. The CV among capsules in individual lots was less than 10.2% for ritonavir and less than 8.9% for all other tested medications.

Conclusions: These quality-control data among generic and branded ARVs are encouraging; they also highlight the importance of storing ritonavir-containing products under continual refrigeration in accordance with manufacturer specifications. Continued quality-control, as well as bioequivalence studies are necessary to identify inferior and/or counterfeit ARVs in developing countries.

INTRODUCTION

- In the developing world at least six of the 42 million HIV-infected patients are in urgent need of antiretroviral medications, yet due to high costs fewer than 300,000 are receiving treatment. However, generic antiretroviral medications along with discounted brand name products are quickly increasing the availability of these drugs.
- Although generic medications offer affordable treatment for many HIV-infected patients, little information is available regarding the integrity of these medications.^{1,3} In a retrospective study, generic nevirapine-containing antiretroviral therapy appeared to be safe and effective among 333 HIV-infected patients in India.² We recently reported that several generic nevirapine formulations from four developing countries contained the labeled amount of drug (\pm 3% of 200 mg).³ Large-scale studies are necessary to assess all antiretroviral medications from international sources for drug content.
- Because of the huge demand and high cost of antiretroviral medications in developing countries, brand name drugs are a likely target for counterfeiters. In an isolated report, an HIV-infected man living in Zimbabwe purchased zidovudine tablets that, upon analysis, were found to contain no zidovudine.⁴ In addition, 60% of tested antimalarial preparations being sold in Cambodia were found to contain either no active ingredient or inferior substitutes.⁵
- To this end, we assessed drug content in comparison to label claims among five HIV protease inhibitors and the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz from various international sources.

METHODS

- Drug products were delivered to the National Institutes of Health (NIH), Bethesda, Maryland and information on individual drug formulations, was recorded (Table 1). All products were received at room temperature and had been stored as such for at least several weeks. Upon receipt, saquinavir, ritonavir, and lopinavir-ritonavir were refrigerated according to manufacturer specifications.
- The Uniformity of Dosage Units test was used to assess the dose uniformity of the different antiretroviral formulations.⁶ This test specifies that drug content in individual dosage units must be within 85% to 115% of the label claim unless otherwise specified in the drug's United States Pharmacopeia/National Formulary (USP/NF) monograph. Saquinavir, the only drug product with a USP/NF monograph in this study, must contain 95-105% of the label claim according to its monograph.⁷
- For quantitative analysis, standards of saquinavir, ritonavir, lopinavir, amprenavir, indinavir and efavirenz were used to prepare calibration and quality control solutions. Serial dilutions of each capsule master stock solution provided test solutions within the standard curve range of the assay, which was 25-9,000 ng/mL for all drugs except for lopinavir, which was 50-9,000 ng/mL. High performance liquid chromatographic (HPLC)/ultraviolet (UV) analysis of each test solution was performed using a validated assay.⁸ Intra- and interday percent error between nominal and observed concentrations was < 10% and %CV% was also < 10%.

RESULTS

- A detailed ingredient analysis, along with specific product information for each of the tested medications is shown in Tables 1 and 2. With the exception of ritonavir-containing products, the active ingredient in each of the products was within 15% of the labeled amount (Range: -12% to + 15%); the absolute value of the mean difference between measured and labeled drug content was 7.7%. The median difference was -2.0%. For efavirenz, indinavir, lopinavir, saquinavir, and amprenavir, expiration dates were available for five of the nine lot numbers sampled (Table 1); among these products, only amprenavir (-7.7% versus labeled amount) was analyzed after its expiration date. The %CV among capsules in individual lots was less than 9.0% for amprenavir, saquinavir, lopinavir, indinavir, and efavirenz.
- Ritonavir content was between -19 and -16% of the labeled amount among one lopinavir-ritonavir and two ritonavir products (Table 1). One of the ritonavir products was analyzed approximately one year after expiring; expiration dates were unavailable for the other ritonavir product and the lopinavir-ritonavir product. As noted earlier, none of the ritonavir-containing products were stored under continual refrigeration in accordance with manufacturer specifications. The %CV among capsules in individual lots was less than 10.2 % for ritonavir.

Table 1. Antiretroviral Product Information

Product ingredient(s) and labeled amount	Trade Name (Manufacturer)	Country where product was obtained	Expiration Date
efavirenz 200 mg	Sustiva (BMS)	Lithuania	not available
efavirenz 200 mg	Stocrin (Merck)	South Africa	not available
indinavir 400 mg	Crixivan (Merck)	Jamaica	not available
indinavir 400 mg	Crixivan (Merck)	South Africa	not available
indinavir 400 mg	Crixivan(Merck)	South Africa	not available
indinavir 400 mg	Indivex-400 (Aurobindo Pharma Ltd.)	Zambia	11/01
lopinavir 133 mg (+ ritonavir 33 mg); <i>same product as below</i>	Kaletra (Abbott)	Lithuania	not available
ritonavir 33 mg (+ lopinavir 133 mg); <i>same product as above</i>	Kaletra (Abbott)	Lithuania	not available
amprenavir 150 mg	Agenerase (GSK)	South Africa	not available
ritonavir 100 mg	Norvir (Abbott)	Lithuania	not available
ritonavir 100 mg	Norvir (Abbott)	South Africa	8/02
saquinavir soft-gel caps 200 mg	Fortovase (Roche)	Lithuania	not available
saquinavir soft-gel caps 200 mg	Fortovase (Roche)	South Africa	not available

DISCUSSION and CONCLUSIONS

- None of the products, when stored according to manufacturer specifications, contained less than 12% or greater than 15% of the labeled drug amount.
- None of the ritonavir-containing products were stored under continual refrigeration; moreover, one of the products had expired. Thus, it is not surprising that ritonavir content did not meet USP content specifications (Table 1b). These data reinforce the importance of storing ritonavir-containing preparations according to manufacturer specifications. This may be particularly true in warmer climates where the ambient temperature is rarely below (77°F [25°C]).
- Studies to determine drug content among branded products from developing nations are also necessary to prevent the dissemination of counterfeit drug products in the developing world.
- Increased availability of antiretroviral medications must be accompanied by independent content analyses studies as well as bioequivalence studies.

Table 2. Antiretroviral Drug Content Analysis

Product ingredient(s) and labeled amount	Mean drug content (%CV)	Average accuracy (versus labeled amount)
efavirenz 200 mg	187.5 mg (4.3%)	94%
efavirenz 200 mg	184.5 mg (5.9%)	92%
indinavir 400 mg	429.3 mg (6.0%)	107%
indinavir 400 mg	437.5 mg (8.8%)	109%
indinavir 400 mg	459.8 mg (8.2%)	115%
indinavir 400 mg	430.1 mg (8.1%)	108%
lopinavir 133 mg (+ ritonavir 33 mg); <i>same product as below</i>	117.7 mg (6%)	89%
ritonavir 33 mg (+ lopinavir 133 mg); <i>same product as above</i>	26.8 mg (10.1%)	81%
amprenavir 150 mg	138.5 mg (4.4%)	92%
ritonavir 100 mg	83.5 mg (8.1%)	84%
ritonavir 100 mg	80.8 mg (6.2%)	81%
saquinavir soft-gel capsules 200 mg	194.2 mg (4.3%)	97%
saquinavir soft-gel capsules 200 mg	197.4 mg (7.3%)	99

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