Hidden costs of antiretroviral treatment: the public health efficiency of drug packaging

Abstract: While the overall percentage of unused antiretroviral medicines returned to the hospital pharmacy is low, their cost is quite high. Adverse events, treatment failure, pharmacokinetic interactions, pregnancy, or treatment simplification are common reasons for unplanned treatment changes. Socially inefficient antiretroviral packages prevent the reuse of drugs returned to the hospital pharmacy. We defined antiretroviral package categories based on the excellence of drug packaging and analyzed the number of pills and costs of drugs returned during a period of 1 year in a hospital-based HIV unit attending to 2,413 treated individuals. A total of 6,090 pills (34% of all returned antiretrovirals) – with a cost of 47,139.91 € – would be totally lost, mainly due to being packed up in the lowest efficiency packages. Newer treatments are packaged in low-excellence categories of packages, thus favoring the maintenance of these hidden costs in the near future. Therefore, costs of this low-efficiency drug packaging, where medication packages are started but not completed, in high-cost medications are substantial and should be properly addressed. Any improvement in the packaging by the manufacturer, and favoring the choice of drugs supplied through efficient packages (when efficacy, toxicity, and convenience are similar), should minimize the treatment expenditures paid by national health budgets.

Keywords: antiretroviral treatment, cost efficacy, drug packaging, treatment change

Introduction

Disbursement in antiretroviral treatment (ART) drugs within the context of a public health shortage of resources has increased the interest in pharmacoeconomic analyses of the available regimens for both treatment-naïve and -experienced individuals.1,2

In Western Europe, the classic concepts of efficacy, effectiveness, and efficiency – supported by the European Medicines Agency’s actions at the time of commercialization – must be completed with equity of care, the efficiency of drug packages, and their potential impact on public health budgets.3

In Spain, there is universal access to ART, and drugs are delivered by law only through hospital-based pharmacies. Not infrequently, patients return opened packages to the pharmacy due to unexpected toxicity, treatment changes, pharmacokinetic interactions, pregnancy, or incomplete adherence.4 The efficiency of these packages, which vary significantly in their quality standards, has an influence on their potential for reuse, and the impact on the cost of treatment for the health system may eventually be considerable.5

Socially efficient packaging in ambulatory care hospital-dispensed drugs should be the one that is best adapted to unit-dose dispensation. In addition, it should facilitate patient compliance, allowing for an easy and hygienic review of the ingested and remaining doses with no need to manipulate either the packaging or the pharmaceutical forms, particularly those that are unused. Moreover, in directly observed ART, drugs that are properly packed permit better control, allowing the delivery of just the
needed doses in every dispensation (ie, adjusted to weekly methadone delivery in drug users).

We established antiretroviral package categories based on the excellence of drug packaging and analyzed the number of pills and the cost of drugs returned during a period of 1 year in a hospital-based HIV unit.

Methods
We defined a classification system for the so-called social efficiency of antiretroviral drug packages that could also be applicable to any other family of high-cost drugs used for outpatients or inpatients (ie, hepatitis C direct antivirals). The classes were as follows:

Class A: Drug packed in unit doses with complete information (name of the drug, dosage in mg, lot number, and expiry date) in each unit, thus maintaining complete information if returned when the external package is opened. No unit doses are opened in the returned packages (Figure 1).

Class B: Drug packed in blisters with complete information only in the blister, but not in every unit dose, without special conservation conditions. Should be initially repackaged in unit doses in the pharmacy before dispensation to ensure class A excellence, with complete tracking information in every unit.

Class C: Drug packed in plastic containers with complete information written only on a label over the container, with no special conservation conditions. It would allow to supply a repackaged drug to the patient.

Class D: Drug packed in plastic containers with any manufacturer’s warning that the product cannot be placed outside of the original package due to special conditions of conservation (fridge, humidity) that will not allow either initial unit dose repackaging or reusing an opened container.

Class B and class C packing increase pharmacy department budgets in terms of human resources, time, and repacking materials. In class D packing, all of the contents will be lost once the container is opened, regardless of being returned.

In order to deliver only the necessary amount of pills until the next visit, or to deliver a predefined schedule of medication via each pharmacy department, class A packages would exhibit optimal social efficiency, whereas class D would demonstrate the worst. Depending on the social efficiency of the drug that patients withdraw, the returned “old” one would immediately become a wasted drug.

The change of a class B or class C drug into a class A drug requires internal pharmacy technician work. The current cost of this change is approximately 0.034€ per pill, according to conditioning material suppliers and human resources obtained through our hospital price list. An experienced technician repackages approximately 214 pills per hour (1,500 pills/day).

Results
The hospital-based pharmacy in our HIV unit served 2,413 treated individuals during the year of study. Patients generated 23,574 visits to the pharmacy during this period, and they experienced a total of 1,051 treatment changes for any reason. Most of the treatment changes were not foreseeable.

The pharmacy department delivered 48,325 antiretroviral drug packages (2,529,137 pills). A total amount of 122,945€ was returned in opened antiretroviral packages. Of these packages, 6,090 pills (34% of all returned antiretrovirals) – with a cost of 47,139.91€ – would be totally lost, mainly due to being packed up in class C and class D boxes. This would be the equivalent to treating 78 individuals with a standard coformulation of rilpivirine/tenofovir/emtricitabine during 1 month.

We have classified all the current ART specialties depending on their social efficiency as supplied in Spain, the UK, and the USA (Table 1). US packaging shows a
greater deal of class C and class D bottles when compared to Europe.

Class A and class B packages returned in bad condition represented only 1.1% of the cost and 75,805€ came from returned packages in good condition that could potentially be reused.

**Discussion**

During a period of 1 year, the percentage of antiretroviral drugs returned to the hospital pharmacy was low. However, the cost of these drugs is high, and therefore there is a significant economic budget loss through unused antiretroviral medicines returned to the hospital pharmacy that cannot be reused due to being supplied in low-excellence packages (approximately one-third of all returned packages).

For hospital inpatients, the excellence in use of ART requires class A packed drugs that allow for administration in unit doses, thus minimizing time hours consumed by nurses in drug administration, reducing medication errors, and improving drug stocks in hospital wards.

The European Commission has singled out specific countries to make particular recommendations to increase the cost effectiveness of the health care sector, and in the case of Spain, there is particular interest in further rationalizing pharmaceutical spending, including ambulatory drugs dispensed in hospitals.

**Table 1** Efficiency class of all antiretroviral drugs available in Spain, the USA, and the UK

| Drug                        | Efficiency class of the packaging | License year, Spain |
|-----------------------------|----------------------------------|---------------------|
|                            | Spain    | US    | UK    |                        |
| Retrovir® 100 mg, 250 mg, or 300 mg | A       | C     | A     | 1987                  |
| Reyataz® 200 mg             | A       | C     | C     | 2004                  |
| Sustiva® 600 mg             | A       | C     | A     | 2002                  |
| Viramune® 200 mg or 400 XR mg | A       | A     | A     | 2011                  |
| Zidovudine® 100 mg, 250 mg, or 300 mg** | A       | N/A   | N/A   | 1996                  |
| Teva-Efavirenz® 600 mg**    | A       | N/A   | N/A   | 2013                  |
| Nevirapine Teva® 200 mg**   | A       | N/A   | N/A   | 2012                  |
| Celsentri® 150 mg or 300 mg | B       | C     | B     | 2007                  |
| Kaletra® tablets            | B       | D     | B     | 2010                  |
| Kivexa® 600–300/Epizicom® I pill once-a-day | B       | C     | B     | 2004                  |
| Trizivir® capsules          | B       | C     | B     | 2001                  |
| Videx® 200 mg, 250 mg, or 400 mg | B       | D*    | B     | 2000                  |
| Zeric® 20 mg, 30 mg, or 40 mg | B       | D*    | B     | 1996                  |
| Ziagen® 300 mg              | B       | B     | B     | 1999                  |
| Lamivudine generic 300 mg (Normon®)** | B       | N/A   | N/A   | 2012                  |
| Combivir® one pill twice daily | B       | B, C  | B     | 1998                  |
| Emtriva® 200 mg             | C       | C     | D     | 2003                  |
| Epivir® 150 mg or 300 mg    | C       | C     | C     | 2002                  |
| Invirase® 500 mg            | C       | D*    | N/A   | 2005                  |
| Isentress®                  | C       | C     | C     | 2007                  |
| Prezista® 600 mg or 800 mg  | C       | C     | C     | 2009                  |
| Reyataz® 200 mg or 300 mg   | C       | C     | C     | 2008                  |
| Sustiva® 200 mg             | C       | C     | C     | 1999                  |
| Telzir® 700 mg/Lexiva® one pill twice daily | C       | D*    | C     | 2004                  |
| Tivicay®                    | C       | C     | C     | 2014                  |
| Viread® 245 mg              | C       | D*    | C     | 2002                  |
| Atripla®                    | D       | D     | D     | 2005                  |
| Crixivan® 200 mg or 400 mg  | D       | D     | D     | 1996                  |
| Edurant®                    | D       | D     | D     | 2007                  |
| Eviplera/Complera®          | D       | D     | D     | 2012                  |
| Intelence® 100 mg and 200 mg | D       | D     | D     | 2008, 2011            |
| Norvir® 100 mg tablets      | D       | D     | D     | 2010                  |
| Stribild®                   | D       | D     | D     | 2013                  |
| Truvada® 200–245 mg one pill once-a-day | D       | D     | D     | 2005                  |
| Triumeq® one pill once daily | D       | D     | D     | 2015                  |

Notes: *“Keep container tightly closed” is specified by the manufacturer in the container. **Generic drugs analyzed only in Spain brands. Abbreviation: N/A, not applicable.
of errors in order transcription and medication administration, and it reduces potential adverse drug events and interactions.7

Establishing strategies to reduce the waste of unused medicines is an unmet need.3,8 Unopened unit dose (class A) drugs that are returned inside the hospitals can be reused. However, in ambulatory care, this reusing is usually not allowed due to the impossibility of granting the quality of drugs once delivered to outpatients.

Unfortunately, newer antiretrovirals—mainly, the new three drug combos, Evipla/Compla, Stiribid, and Triumeq— are commonly packaged in class C and class D categories, thus promoting the maintenance of these hidden costs in the near future. Any improvement in the excellence of packaging by the manufacturer, and favoring the choice of drugs supplied through more efficient packages (whenever efficacy, toxicity, and convenience are similar), should minimize treatment expenditures paid by national health budgets.

Conclusion
In summary, while the overall percentage of unused antiretroviral medicines returned to the hospital pharmacy is low, their cost is quite high. Therefore, the hidden costs of this low-efficiency drug packaging in wasted drugs in these kinds of medications are substantial and should be properly addressed.

Drug regulatory authorities should consider including the concept of social efficiency of the packaging in the authorization process of high-cost specialty medicines delivered through hospital dispensing to ambulatory patients, as many of these drugs are actually manufactured in Europe.

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Author contributions
AAC and JML wrote the first draft of this manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure
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