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Legal, ethical, and economic implications of breaking down once-daily fixed-dose antiretroviral combinations into their single components for cost reduction

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ABSTRACT

The availability of generic lamivudine in the context of the current economic crisis has raised a new issue in some European countries: breaking up the once-daily fixed-dose antiretroviral combinations (FDAC) of efavirenz/tenofovir/emtricitabine, tenofovir/emtricitabine, or abacavir/lamivudine, in order to administer their components separately, thereby allowing the use of generic lamivudine instead of branded emtricitabine or lamivudine. The legal, ethical, and economic implications of this potential strategy are reviewed, particularly in those patients receiving a once-daily single-tablet regimen. An unfamiliar change in antiretroviral treatment from a successful patient-friendly FDAC into a more complex regimen including separately the components to allow the substitution of one (or some) of them for generic surrogates (in the absence of a generic bioequivalent FDAC) could be discriminatory because it does not guarantee access to equal excellence in healthcare to all citizens. Furthermore, it could violate the principle of non-maleficence by potentially causing harm both at the individual level (hindering adherence and favouring treatment failure and resistance), and at the community level (hampering control of disease transmission and transmission of HIV-1 resistance). Replacing a FDAC with the individual components of that combination should only be permitted when the substituting medication has the same qualitative and quantitative composition of active ingredients, pharmaceutical form, method of administration, dosage and presentation as the medication being replaced, and a randomized study has demonstrated its non-inferiority. Finally, a strict pharma-economic study supporting this change, comparing the effectiveness and the cost of a specific intervention with the best available alternative, should be undertaken before its potential implementation.

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Implicaciones éticas, legales y económicas de la sustitución de las coformulaciones antirretrovirales a dosis fijas tomadas una vez al día por sus componentes por razones de reducción de coste

RESUMEN

La disponibilidad de lamivudina genérica en el actual contexto de crisis económica ha sacado a la luz una nueva discusión en los países europeos: la sustitución de las combinaciones antirretrovirales a dosis fijas tomadas una vez al día (CADF) de efavirenz/tenofovir/emtricitabina, tenofovir/emtricitabina o abacavir/lamivudina, con la finalidad de administrar sus componentes por separado, lo que supone permitir el uso de lamivudina genérica en lugar de la emtricitabina o la lamivudina de marca. Se revisan las implicaciones legales, éticas y económicas de esta estrategia potencial, en particular en aquellos pacientes que tienen un régimen de una única pastilla una vez al día. Un cambio no consensuado en el tratamiento antirretroviral, pasando de una CADF exitosa y cómoda para el paciente a un tratamiento más complejo que incluya los componentes por separado para permitir la sustitución de uno (o varios) de ellos por los genéricos (en ausencia de una CADF genérica bioequivalente) podría ser discriminatorio porque no garantiza el acceso a un igual tratamiento de excelencia a todos los ciudadanos. Además, podría violar el principio de no maleficencia, causando potencialmente daño tanto a nivel individual

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(dificultando la adherencia y favoreciendo el fracaso y la resistencia al tratamiento) como a nivel comunitario (dificultando el control de la transmisión de la enfermedad y la transmisión del VIH-1 resistente). Reemplazar una CADF por los componentes individuales de dicha combinación únicamente debería estar permitido cuando la medicación de sustitución tenga la misma composición cualitativa y cuantitativa en sus ingredientes activos, forma farmacéutica, método de administración, dosis y presentación que el medicamento que va a ser reemplazado, y cuando un estudio aleatorizado haya demostrado su no inferioridad. Por último, un estricto estudio farmacoeconómico apoyando este cambio, comparando la efectividad y el coste de una intervención específica con la mejor alternativa disponible, debería llevarse a cabo antes de su potencial implementación.

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Introduction

Antiretroviral therapy (ART) persistently suppresses HIV-1 replication, allows gradual recovery of CD4⁺ T-cell lymphocyte counts, and reduces or even averts patient morbidity and mortality.^{1–5} These treatments revert the ominous prognosis of HIV-1 disease and drastically cut down the risk of transmission to the general population, supporting the concept of “treatment as prevention”.^{6,7}

Achieving and maintaining viral suppression require the life-long use of regimens with preferably three active drugs from two or more drug classes, thus challenging continued patient's adherence.⁸ Poor adherence to ART increases the risk of incomplete viral suppression and treatment failure, disease progression, transmission to the general population of both HIV-1 infection and drug resistance, and death.^{9,10} ART has improved steadily since the advent of potent combination therapy in 1996. Regimens have evolved from those involving administration of >25 pills and 3 times per day to those involving 1 pill administered once-daily, associated with better adherence rates.^{8,11,12} Decreasing the toxicity, pill burden, and dosing frequency is associated with increased adherence and is strongly recommended in all treatment guidelines.^{8,13–15} In the absence of overriding considerations, cost and affordability should also be considered.¹³

Fixed-dose antiretroviral coformulations (FDAC) are pivotal in reducing the risk of treatment errors and selective non-compliance, and their use has been associated with higher adherence rates and lower risks of hospitalization, both in challenging homeless and marginally housed people, as well as in US Medicaid enrollees and in the US Lifeline database.^{16–19} Single-tablet regimens (STR) taken once-daily are the utmost level of treatment simplification, and in difficult-to-treat populations have also demonstrated better adherence rates than non-one-pill-once-daily regimens.²⁰ With the exception of those cases where dose adjustment is required, the preferential use of FDACs is recommended in those situations where the agents included in the coformulation are drugs of choice.^{8,15}

As costs of care for HIV-infected subjects rise, National policy makers must determine the most efficient and cost-effective methods for managing HIV disease.^{20,21} With more than 70% of all costs of HIV disease coming from ART, further scrutiny of drug pricing and utilization is to be expected.²² The cost-effectiveness variable should be measured in order to provide a more transparent decision about which treatment would be covered, which price would be paid and which clinical situations and groups of patients would be eligible.²³ A way must be found to resolve a basic dilemma: cost controls that are likely to be politically acceptable will not be very effective, and what might be effective will not be acceptable.²⁰ In Spain, costs and cost-efficacy analysis of the preferred antiretroviral treatments recommended in the National guidelines are analyzed yearly and results are systematically reported in medical journals.²⁴ Generic drugs dramatically lower the cost of care also in HIV infection.²⁵ ART regimen costs have nevertheless not been significantly reduced so far in developed countries with the availability of

generics, because newer patent-protected drugs were assumed to continue to be preferred based on efficacy and convenience.^{8,12,22} Recent mathematical models have estimated that in the near future generic-based ART in the United States could yield substantial budgetary savings to HIV programs.²⁶ Compared with a slightly less effective generic-based regimen, the cost-effectiveness of first-line branded ART would exceed an unacceptable ratio of \$100 000/QALY, thus favouring the use of generics without any doubt.

FDACs currently have in Europe the same cost of their branded components administered separately. However, the availability of generic lamivudine in the context of the current economic crisis has raised a new issue in some Spanish public hospitals: breaking up the once-daily FDAC of efavirenz/tenofovir/emtricitabine, tenofovir/emtricitabine, or abacavir/lamivudine, in order to administer their components separately and thus allowing the use of generic lamivudine instead of branded emtricitabine or lamivudine. Thus, the change is not that of an ART based on a brand FDAC towards a bioequivalent generic FDAC, but of a brand FDAC towards the separated components, generic or branded, included in the coformulation. This brings up a new challenge in the history of ART.

This paper attempts to determine the legal, economic, and ethical implications associated with a change in the treatment of HIV-1-infected subjects receiving a FDAC, and particularly those receiving a once-daily STR, to a split treatment administering the components separately, including generic surrogates of some components. These implications are focused in Spain but they can also be exported to Europe and US.

In what way does an unconsented change to a more complex pharmacological treatment schedule affect the patient's right to choose his/her treatment?

HIV is an infection that does not allow people to play around when discussing treatments. Whether by means of a brand name or a generic ART, based on a FDAC or not, the difference between having access or not to ART can drive the difference between living or not.^{27,28}

In Spain, the EU and the US the law recognizes the patient's right to not to be given a treatment without previous consent.^{29–31} The patient has the right to freely decide, after receiving adequate information, between the available clinical options, and s/he also has the right to refuse treatment, except in cases where a public health risk is present or there is immediate serious risk to the patient's health or to the transmission to a third person, as would be the case in a HIV-infected pregnant women to prevent mother-to-child transmission.³² In addition, the physician must fulfil his/her duty to provide the patient with the pertinent information about benefits and drawbacks of the treatment change, when choosing or changing the ART according to the clinical situation, including treatment changes from FDAC to the split elements of the coformulation.²⁹

The right to consent treatment, however, does not include the right to choose between a branded medication and a generic one. The principle of rational use of medications implies the preference

of prescription by active ingredient.³³ Generic medicines are products with demonstrated bioequivalence to the branded ones, and which are more economical because the original period of medication exclusivity (patent) has expired. They ensure identical conditions of quality, safety, and effectiveness at a lower price to the community. As a general rule, authorized generic medications cannot be sold until ten years after the date of the initial authorization of the reference branded medication.³⁴

It has been very well documented that generic antiretrovirals are fully effective and also reduce the mortality and morbidity rates associated with HIV in places where their use is widespread.^{8,27,28} Thus, it is pertinent to know what should be done when a FDAC has no generic FDAC surrogate including the same bioequivalent generic components, and therefore the aim is breaking down the pharmacological treatment based on that FDAC.

On the legal level, in the EU, the Directive 2001/83/CE states the basic guidelines on medicinal products for human use. Article 10 regulates generic drugs in the EU internal market establishing the principle of interchangeability, whereby a branded drug can be substituted for a generic drug if it meets three conditions: (i) the same qualitative and quantitative composition in active substance(s) as the reference product, (ii) the same pharmaceutical form as the reference medicinal product, and (iii) whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.³⁵ All the state members of the EU follow this. For example, both the laws in Spain,³³ France,³⁶ and Germany³⁷ state that a generic medication is one that has the same qualitative and quantitative composition in active substances, the same pharmaceutical form, and its bioequivalence with the reference medication has been demonstrated by studies adapted to bioavailability.^{36,37} Also in the USA we can find the same regulatory principle in the Drug Price Competition and Patent Term Restoration Act, also known as Waxman-Hatch Act.³⁸

According to the National, European, and US legislations, the substitution of a prescribed medication (a FDAC) is only permitted on the condition that the three cumulative requirements are met. If one of the three requirements is not met, the substitution cannot be made. The problem here is that there is not a generic FDAC, so the principle of interchangeability cannot be applied.

Finally, even though lamivudine and emtricitabine are similar molecules, they have differential characteristics that do not allow us to rule out the possibility of different resistance rates in the event of virological failure, and even the overall failure rates, as has been seen in a recent metanalysis when administered with tenofovir-containing regimens.^{17,39–42} Furthermore, clinical trials have only included one of them and we have no head-to-head comparisons. Thus, the efficacy of replacing emtricitabine with lamivudine remains uncertain.

The unconsented substitution of a successful FDAC to a less convenient one in some areas of a given country could breach the principle of equality and non-discrimination

The change could breach the principles of equal treatment and non discrimination that are recognized in the Spanish Constitution and are as well the rule of European States and US (art. 43, 9, and 14).⁴³ The change would violate the rights of all citizens to obtain medications in equal conditions throughout all the Spanish Healthcare System (Spanish NHS).⁴⁴ This constitutional principle has higher hierarchy than the measures intended to rationalize the prescription and use of medications that the National and local healthcare administrations in a given country might adopt. Actually, the Spanish law guarantees equally effective conditions throughout the National territory, allowing for the free movement of all citizens and receiving the same excellence in treatment.^{43,44}

All people are considered equal with no relevance given to the place within the National territory where they reside, in particular, taking into account the special characteristics of the island territories. Although, Autonomous Communities have legal competence in healthcare issues, the National government establishes a minimum uniformed regulation in order to impede discrimination in matters of health that could affect any group which might have special difficulty (e.g. based on the place of residence) in gaining real and effective access to them.

The Spanish NHS's catalogue of benefits is designed to guarantee the basic common conditions for complete, continuous attention at a proper level, defining the healthcare coverage offered to all citizens.⁴⁵ Concerning the pharmaceutical benefits, ART and FDAC are indeed included in the catalogue of medications and all of the measures must be taken to ensure that patients receive medication in a universal manner that is adequate to their clinical needs, in the precise dose to meet their individual requirements, during an adequate period of time, and at the lowest cost possible for them and for the community, and irrespective of the place of residence.

Within the lists of services, each Autonomous Community must include, as a minimum, all of the services listed by the Spanish NHS. This minimum content is not optional and must be regularly adapted to technological advances and to the needs of the population covered by the Spanish NHS.⁴⁴ Otherwise, the level of excellence of ART that two citizens in the same situation would receive in the same country would vary depending on the catalogue approved by the Autonomous Community where they reside or the hospital where they are treated based only on economic criteria in spite of having a common healthcare system. That would be a violation of the rule of law and the principle of equality, resulting in discriminatory treatment because the same situation would be treated unequally without an appropriate rational justification, according to the jurisprudence of the Spanish Constitutional Court, the European Court of Human Rights and the US Supreme Court.^{46–48}

The change of a successful FDAC into a more complex regimen may harm both at the patient and community levels, in that it may affect patient's adherence and lead to the appearance of treatment failure and resistance

Breaking up a successful and more patient-friendly FDAC, changing to another regimen using the same components separately in order to administer one or some of them as generics (when the equivalent generic FDAC is not available), may harm or be detrimental not just to the own patient, but it may also make the community's control of the disease more difficult.^{6,7} In this case, it would be violating the ethical principle of non-maleficence that requires that any action that leads to harm or increases the risk of harm occurring be omitted.⁴⁹

This treatment switch might represent a step backward in advances made in simplicity and adherence to ART, and would carry the risk of a patient selectively not taking one of the medications (selective non-compliance), which would then be administered separately. FDACs proved to be a significant advance in simplifying ART, facilitating the use of complex regimens in chronic illnesses and resulting in a measurable improvement in adherence and patient's quality of life.¹⁷ Not surprisingly, patients do prefer the simplest ART possible. In HIV disease, irregular adherence and covert monotherapy, even for just a few months, may lead to the permanent loss of effectiveness of the therapeutic regimen, the development of resistance to the drugs the patient is receiving, and even cross-resistance to other future medications. Thus, FDAC may contribute to reducing the risk of the development of HIV-1 resistance to antiretroviral drugs, which would not only compromise

treatment options for the individual, but would also increase the probability of transmission of both HIV-1 infection and resistance to serodiscordant couples.^{6,7,17,50} The control of HIV replication has positive consequences not only at the individual level, but also on a societal level, since it drastically reduces the risk of transmission by treated individuals to their couples, the general population, and it avoids vertical transmission from infected mothers to their children.^{8,51,52}

FDAC reduce the number of different packages and medications that the patient must keep track of,¹² a strategy used in all chronic illnesses requiring a combined treatment in order to reduce the risk of confusion and selective non-compliance. Actually, the widespread use of FDAC has been correlated with a decrease in the prevalence of HIV-1 drug resistance mutations at a population level.⁵³

FDAC are preferred regimes in all ART Guidelines.^{8,13–15} Both Spanish, European, and American consensus documents recently updated an entire section dedicated to treatment simplification, understood as the change from one therapeutic plan that has managed to safely suppress the viral replication to another one that is simpler and continues to produce that suppression and has some added benefit for the patient. The objectives are to improve the quality of life, facilitate adherence to the plan, and prevent or reverse some adverse side effects. With simplification we can reduce the number of drugs involved, the number of pills, frequency of doses, and take advantage of the convenience of coformulations. New classes of antiretroviral drugs along with the development of FDAC have greatly contributed to developing simpler treatments. Simplification has been a highly used strategy for a long time, but at present, simpler therapies from the beginning are the usual practice, leaving a few left to be simplified.⁸

The change of a successful pharmacological treatment for cost reduction may only be justified if the overall costs are considered

It has not yet been established how the breakage of FDAC fits in with the principle of rational use of medication based on cost reduction. Some preliminary reports have shown that unlike the desired objective of cost-saving, FDCAs disruption might lead to an increase of health care expenditure due to an unexpectedly high rate of adverse events and hospital visits, probably related to the lack of obtaining patient's informed consent.⁵⁴ At the contrary, in a recent analysis done in Denmark with 529 patients, in a well organized health care setting with free access to antiretroviral therapy, a switch from coformulated efavirenz/tenofovir/emtricitabine tablet to a cheaper multi-tablet regimen for economic reasons did not reduce virological response.⁵⁵

The improvements achieved with ART come at a cost. Antiretroviral drugs have a high price due to, among other factors, the investment done in order to obtain the new products. ART constitutes one of the most cost-effective therapeutic strategies available in the western world.^{1,5,8,22,25,56} As a consequence of the improvements accomplished in life expectancy and quality of life, there has been a significant decrease in the use of health services (both at hospital and ambulatory levels) related to HIV disease, as well as a decrease in the spread of HIV-1 infection. The majority of the economic evaluations in this area have focused only on drug costs, some of them on determining the direct costs (prevention, diagnosis, and treatment), and very few have included indirect costs (loss of productivity, HIV transmission).⁵³ Actually, an antiretroviral treatment consisting of a single pill per day was associated with significantly better adherence and lower risk of hospitalization in HIV-infected patients compared to patients receiving three or more pills per day in a recent analysis done in 7073 US patients.¹⁶

Patients receiving a single pill per day were 24% less likely to have a hospitalization versus those receiving three or more pills per day (OR = 0.76; $p = 0.003$). In agreement with this, another analysis done in 7825 US patients who received a complete antiretroviral regimen between June 1, 2009 and December 31, 2011, also demonstrated that non-STR combinations have twice the risk of incomplete daily dosing vs. an STR, and are associated with an additional significant risk of hospitalization which ranged from 43 to 54% ($p < 0.0001$).¹⁹ Therefore, receiving antiretroviral treatment as a single pill per day was associated with potential clinical and economic benefits. Thus, a strict pharma-economic study supporting this change should be done before implementing it.

Conclusion

In summary, an unconsented pharmacological change from a successful patient-friendly FDAC into a more complex regimen including separately the components to allow the substitution of one (or some) of them for generic surrogates (in the absence of a generic bioequivalent FDAC) could violate the principle of equality and non-discrimination in the access to excellence in the health services throughout a Nation territory; can cause harm both at the individual level (lack of adherence and the appearance of treatment failure and resistance) and at the community level (hinders control of disease transmission); and, finally, could increase the costs if indirect costs of the switch are taken into account.

Substituting a FDAC with the individual components of that combination is only permitted when the substituting medication has the same qualitative and quantitative composition of active ingredients, pharmaceutical form, method of administration, dosage and presentation as the medication being replaced.

Conflicts of interest

Miguel A. Ramiro has received payment for conferences and legal counselling from CESIDA. He is member of the research project 'El tiempo de los derechos', Consolider-Ingenio 2010, funded by the Ministry of Science and Innovation (CSD2008-00007).

Josep M. Llibre has received funding for research or payment for conferences or participation on advisory boards from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme, Tibotec, and ViiV Healthcare.

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