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Utilization and costs of HIV antiretroviral drugs in Europe during the last ten years: Impact of generic antiretroviral drugs on cost reduction

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ABSTRACT

Introduction: Simulation studies showed that generic antiretroviral (ARV) drug utilization could lead to significant cost reduction of HIV treatment in developed world. This study aimed to quantify ARV utilization and costs in European countries between 2006 and 2015. We also assessed the impact of generic ARV drug utilization on cost reduction in real-life.

Methods: ARV drug utilization in 14 European countries (France, Italy, Germany, Denmark, Netherlands, Norway, Sweden, Finland, Iceland, Croatia, Czech Republic, Estonia, Latvia, and Lithuania) were analysed using defined daily dose (DDD)/1000 inhabitants/year. ARV drug cost was estimated in million euro/year and euro/1000 inhabitants/year. The impact of generics on cost reduction was assessed in three countries: France, Denmark, and Czech Republic, using four parameters: *expected savings, observed savings, brand price-reduction savings* and *overall savings.*

Results: Between 2006 and 2015, median ARV drug utilization increased from 234 DDDs per 1000 inhabitants per year (IQR 124–388) to 385 (229–670). The median cost increased from €3751/1000 inhabitants/year (1109–4681) to €9158 (3269–10,646). Between 2013 and 2015, overall savings of €0.9, €1.6, and €33.7 million were respectively observed in Denmark, Czech Republic, and France.

Conclusion: Overall savings observed in real-life from generic ARV drugs in Denmark were related to high rate of low-price generic utilization, contrarily to France and Czech Republic where these were more related to brand price-reduction than generic utilization itself.

1. Introduction

Since the introduction of Highly Active Antiretroviral Therapy (HAART), HIV infection has become a manageable disease and life expectancy of HIV-infected people considerably increased [1–4]. However, the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO) noted a stable incidence of HIV infection the last ten years, according to the 2015 report [5] and a significant increase in the number of new HIV cases in Europe the past three years [6]. The Global Burden of Disease (GBD) study 2015 also reported constant incidence of HIV infection and reduction of mortality in people living with HIV leading to an increase of HIV prevalence [7]. Furthermore, current WHO guidelines recommend treatment of all HIV positive people regardless their immune status [8] and use of the fixed-dose combination (FDC) of emtricitabine and tenofovir disoproxil fumarate (FTC/TDF) for HIV infection prevention [9]. Consequently, HIV antiretroviral (ARV) drug utilization and costs are likely to continue increasing in European countries.

Since 2009, generic ARV drugs have been approved by the European Medicine Agency (EMA) and started being marketed in Europe later in 2013. Among them: lamivudine (150 mg and 300 mg: 3TC) was approved in 2009, the FDC of zidovudine 200 mg/lamivudine 150 mg (AZT/3TC) in 2011, nevirapine 200 mg (NVP) in 2009, efavirenz 600 mg (EFV) in 2012, tenofovir disoproxil fumarate 245 mg (TDF) in 2016 (but was initially available in Czech Repub-

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lic from 2014), and lopinavir/ritonavir (LPV/r) approved in 2016. Other patents expiry are expected during the next years, e.g.: abacavir 300 mg (ABC) in 2017, FTC/TDF in 2024, etc. and this could lead to marketing of other generic drugs in the future [10]. Current marketed generic ARV drugs do not include single-tablet regimens (STR). Therefore, they are likely to substitute brand drugs incorporated in multi-tablet regimens (MTR) without breaking FDCs or modifying the pill-burden (e.g.: substitution of the brand of (AZT/3TC) by the generic of (AZT/3TC)), or by breaking single-tablet regimens (STR) leading to the increase of pill-burden (e.g.: substitution of EFV 600 mg incorporated in the brand STR of efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF) by the generic EFV 600 mg plus the brand (FTC/TDF)) [11].

Studies recommended utilization of generic ARV drugs in developed countries for lowering the cost of HIV treatment [12,13]. In addition, simulation studies have been performed to assess the expected cost reduction related to the introduction of generic ARV drugs: one study reported savings of up to $920 million the first year and a lifetime average savings of $42 500 per eligible patient in the USA [14], one other reported a cost reduction of £1·1 billion between 2015 and 2019 in the UK [15]. In other European countries, such studies reported a cost saving expected between 1·6% and 31·8% in Germany [16] and up to €76 million annually in Italy [17]. Furthermore, other studies have shown that 75% of doctors were willing to prescribe and 44% of patients to take generic ARV drugs in France [18]. Forty nine percent of patients in the Netherlands were also willing to take multi-tablet regimens that incorporate generic ARV drugs instead of STR.[19] However, there are few data regarding utilization of ARV drugs at the European level, neither data investigating the spreading of their generics since their first introduction in 2013.

In Europe, there are several data sources available to conduct drug utilization studies. However, access and data availability are widely differ across countries, as identified by the IMI PROTECT project [20]. This program aimed to identify and collect different data sources able to perform drug safety studies at the European level. The study by Brauer et al. [21] performed among seven health care databases available in five different countries aimed to estimate the prevalence of and characteristics of anti-infectious drugs in ambulatory care. However, to the best of our knowledge, none of the studies performed in this context investigated the patterns of use of ARV drugs in different European countries. Thus, our study aimed to analyse the level of ARV drug utilization in different European countries from public health care data sources and evaluate the real impact of generic ARV drug use on cost reduction in real-life settings.

2. Materials and methods

The first step was to identify publicly available data regarding ARV drug utilization and related costs in different European countries. ARV drug utilization and/or cost data were collected in 14 European countries for the period between 2006 and 2015. Nationwide annual reports and databases of medicines utilization (dispensed or sold quantities) and related costs with free access were used for data collection. Collected data were related to sales from wholesalers in (Croatia, Czech Republic (2006–2011), Estonia, Finland, Iceland, Latvia, and Lithuania), prescriptions dispensed by community pharmacies in (Czech Republic (2012–2015), France, Germany, Netherlands, Norway, and Sweden) and prescriptions dispensed by community pharmacies or others including hospitals (Denmark, Italy) [22,23]. The specification on whether the item dispensed was brand or generic ARV drugs was available in only three countries: Denmark, France, and Czech Republic. ARV drug cost data were obtained for ten countries (Croatia, Czech Republic, Denmark, France, Finland, Germany, Italy, Netherlands, and Norway) (Supplementary Table S1).

For each drug, we computed the total quantity dispensed or sold per year in number of defined daily dose (DDD) according to the WHO Collaborating Centre for Drug Statistics Methodology published in 2003 [24]. Drug utilization was presented as the number of DDD per 1000 inhabitants per year. Generally, the WHOCC recommends the use of DDD per 1000 inhabitants per day, but due to the relatively low level of use, we chose the formulation proposed by Norway [25] presenting ARV drug utilization in DDD per 1000 inhabitants per year. Thus, instead of quantifying drugs (DDDs) consumed by 1000 inhabitants per day (according WHO method), we quantified the quantity (DDDs) of drugs consumed by 1000 inhabitants per year. We also computed the ARV drug expenditures in millions of euros per year and in euro per 1000 inhabitants per year, with specification of expenditures corresponding to generic drugs when this information was available. European median of drug utilization (cost) was defined as the sum of ARV drug utilization (cost) per 1000 inhabitants per year in countries where these data were available divided by the total number of these countries.

The impact of generic ARV drugs on cost reduction was measured using four parameters: 1) *Expected savings* defined as the difference between costs if all dispensed (sold) ARV drugs, substitutable by generics, were brands and costs if all dispensed (sold) ARV drugs, substitutable by generics, were generics; 2) *Observed savings* defined as the difference between costs if all dispensed (sold) ARV drugs substitutable by generics were brands and costs observed; 3) *Brand price-reduction savings* defined as the difference between cost if all dispensed (sold) brand ARV drugs substitutable by generics were sold at their price before the introduction of corresponding generics and observed costs, and 4) *Overall savings* defined as the sum of observed savings and brand price-reduction savings.

Brand ARV drugs considered for the estimation of the impact of generic ARV drugs on cost reduction were (3TC), (AZT/3TC), (NVP), (EFV), and (TDF) that are substitutable by their generics without breaking fixed-dose combinations (FDC). Statistical analyses were conducted using Excel and SAS version 9·4 (SAS Institute, Cary, NC, USA) software.

3. Results

3.1. Utilization and cost of antiretroviral drugs in Europe between 2006 and 2015

Between 2006 and 2015, the overall median of ARV drug utilization increased from 234 DDDs per 1000 inhabitants per year (IQR 124–388) to 385 (229–670) and median cost from €24 million euro (IQR 7–280) to 50 (24–410), equivalent to €3751 (1109–4681) and €9158 (3269–10,646) per 1000 inhabitants per year (Supplementary, Fig. S1). Five European countries (Estonia, France, Italy, Netherlands, and Denmark) reported a higher ARV utilization level than the European average (Fig. 1a) and five others (Latvia, Czech Republic, Norway, Sweden, and Germany) an ARV utilization level closer to the European average (Fig. 1b). For four others (Iceland, Finland, Croatia, and Lithuania) ARV drug utilization was below the European average (Fig. 1c).

The highest cost of ARV drugs per 1000 inhabitants per year in Europe in 2015 were observed in France (€15,170), followed by Netherlands (€10,821), Italy (€10,469), Denmark (€10,220), Norway (€8096), Germany (€7560 in 2013), and Iceland (€7 167 in 2013). In France, the total cost of ARV drugs exceeded one billion euro in 2015. ARV drug costs per 1000 inhabitants per year were moderate in Finland (€4286) and relatively low in Czech Republic (€2252), and Croatia (€1110) (Fig. 2).

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