Impact of Generic Antiretroviral Drugs Introduction on Pharmaceutical Expenditure Patterns in the Netherlands: A Six-Year Retrospective Database Analysis from 2016 to 2022

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Abstract

Background

In the Netherlands, the annual expenditure on HIV care was 202 million euros in 2019, with about 70% allocated to antiretroviral therapy (ART). The introduction of generic antiretroviral medications (ARVs) in 2017 has offered potential cost-saving opportunities in healthcare. Understanding the financial implications of incorporating generic ART into the Dutch healthcare system is crucial to determine its impact.

Methods

We used data from the Foundation for Pharmaceutical Statistics (SFK), covering 98% of all community and outpatient clinic pharmacies across the Netherlands. This dataset contained medication information from 2016 to 2022. Medication data were classified using the Anatomical Therapeutic Chemical Classification with Defined Daily Dose (ATC/DDD) system. Cost analysis was based on Dutch drug prices (www.medicijnkosten.nl) for a specified period, and the data were processed using IBM SPSS.

Results

In the Netherland, people with HIV receiving ART increased from 20,072 to 24,573 between 2016-2022. HIV medication expenditure was 191 million euros in 2016, with generic medication at 6% DDDs. After an increase in 2017, a subsequent decrease in total HIV medication expenditure led to an overall cost of 180 million euros in 2022 (-9.4% compared to 2016). Simultaneously, the proportion of DDDs with a generic increased to 16-32% over the years. This could be linked to 97% compliance with generic substitutions for ARVs where a generic equivalent was available. Notably, the cost per patient per year has declined from €9,488 in 2016 to €7,352 in 2022 (-22.5% compared to 2016). Some of the potential cost-savings through generic substitution were not utilized because of the 20% increase in the use of novel branded single-tablet regimens (STRs).

Conclusions

Our analysis showed high compliance with generic substitution of ARVs in the Netherlands. The increased use of generic ARVs was accompanied by an almost 10% reduction in overall expenditure on ART costs despite a significant increase in the number of patients in care in the Netherlands during this period. A significant contributing factor to ART costs appears to be the high percentage of prescribed patented Single-Tablet Regimens (STRs). These findings underscore the complex dynamics of pharmaceutical expenditures in the Dutch healthcare system.

Introduction

The number of people receiving care for HIV is steadily increasing, and people with HIV are living longer [1]. Although these developments are positive, they also introduce financial challenges. In the

Netherlands, 89% of people with HIV (94% of those diagnosed and linked to care) used antiretroviral therapy (ART) in 2021 [1]. Consequently, without intervention, the costs of ART will continue to increase. The expenses associated with ART pose a significant problem within the framework of healthcare expenditures, particularly due to the fact that medications account for 70% of the HIV healthcare costs [2]. Finding ways to control costs without compromising quality of care is vital for ensuring sustainable and accessible HIV treatment [3, 4].

Since late 2017, the availability of generic antiretroviral (ARVs) medications in the Netherlands has led to significant changes in HIV treatment. Generic medications offer a more cost-effective alternative than their branded counterparts do. The introduction of generic options has expanded the range of choices for healthcare providers, allowing them to prescribe medications that are equally effective but at a lower cost [5].

In the Netherlands, healthcare providers are free to choose any specific medication for each person with HIV. However, when a generic version is prescribed, the decision regarding which generic product to prescribe is determined by the health insurance provider [6]. This approach ensures cost awareness while maintaining treatment efficacy and quality of care [7].

To explore the economic impact of introducing generic ARVs in the Netherlands on total pharmaceutical expenditure, we conducted a retrospective database study. This study aims to answer several questions. First, we sought to determine the annual total pharmaceutical expenditure for ART. Second, we examined the uptake and utilization patterns of generic ARVs over time. Third, we assessed the impact of generic ARVs on overall pharmaceutical expenditures. Finally, we aim to estimate the potential cost savings achievable using generic ARVs.

Methods

Data source and period

We used data from the Foundation for Pharmaceutical Statistics (Dutch: Stichting Farmaceutische Kengetallen, SFK), which has been collecting medication usage data in the Netherlands since 1990. This dataset was derived from a panel of pharmacies, representing over 98% of all community and outpatient clinical pharmacies in the Netherlands. It includes detailed records of medication dispensations, pharmacies, insurance involvement, prescribers, and patient information, and adheres to strict privacy guidelines [8].

The observational period of the study began in January 2016 since one year later, and generic formulations of some widely used ARVs were introduced in the Netherlands. Therefore, 2016 can be used as the starting point for these analyses. Data from the SFK are available until December 2022.

Data structure and editing

The dataset comprised all ARVs identified by their Anatomical Therapeutic Chemical (ATC) classification codes and distributed on a monthly basis, irrespective of their use for HIV prevention or treatment [9]. Additional variables included pseudonymized patient codes, year of birth, gender, date of issue of medication, article number, article name, ATC code and description, preference status for health insurance, delivered quantity, unit of quantity, patent status, pharmacy retail price, and defined daily dose (DDD). DDD was calculated as the daily per capita consumption of each specific antiretroviral substance, categorized by ATC, in accordance with the manufacturer's specifications and guidelines [10]. The ATC codes considered were categorized by substance class, specific antiretroviral substances, and the quarter/year of their introduction as generic drugs (Table 1) [11]. In Table 2, we have summarized the prices of all generic ARVs per year, aligning each price with the respective year. We used the Dutch medicine prices with the corresponding years [12].

To prepare the database for the analysis, we implemented several exclusion criteria. First, we excluded instances of non-chronic use or single supplies of ARV medications in any of the six consecutive years. Examples of non-chronic use were prescriptions for post-exposure prophylaxis (PEP), mainly comprising dolutegravir (DTG) combined with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), foreign travelers, expats, etc. Second, we excluded prescriptions intended for the treatment of hepatitis B, including tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF), and lamivudine (3TC). Finally, we excluded all prescriptions related to pre-exposure prophylaxis (PrEP) regimens consisting of TDF/FTC, ensuring that only unique prescriptions per individual were considered in our analysis.

Table 1: Anatomical Therapeutic Chemical (ATC) classifications of antiretroviral drugs

a according to the WHO Collaborating Centre for Drug Statistics Methodology

b based on information from the Summary of Product Characteristics (SmPC)

* introduction of nevirapine prolonged release (introduction of immediate release was 09/2011)

Table 2: Generic introductions of antiretroviral drugs in the Netherlands, with lowest pharmacy purchase price (€)

* calculated with a defined daily dose of atazanavir of 300 mg and darunavir of 800 mg

Statistical Analysis

We conducted an exploratory data analysis to assess costs per patient, generic ARV utilization, and cost savings. Descriptive and historical analyses focused on primary outcomes, including ARV costs and generic drug utilization, whereas secondary analyses explored the financial implications of generic ARV substitution strategies.

Determination of cost-savings and potential cost-savings

First, we identified ARV medications that became available in generic form during the study period. Subsequently, we assessed the distribution of branded versus generic medications within this timeframe, considering the defined daily dose (DDD) in conjunction with the calendar year. To calculate the proportion of generic medications based on price, we divided the total expenditure for each ARV per year by the DDD, resulting in a price per DDD for each ARV per year.

To evaluate the cost savings and potential cost savings, we initially examined the cost reductions for each ARV by comparing the price per DDD in 2022 with that in 2016. To demonstrate an example of how generic ARVs could further contribute to cost savings, we performed a sub-analysis of persons with HIV on single-tablet regimens (STRs) that had the potential to be split using an nucleoside reverse transcriptase inhibitors (NRTI) backbone as generic components. This is mainly related to STRs that contain either dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) or rilpivirine/tenofovir disoproxil fumarate/emtricitabine (RPV/TDF/FTC). In this sub-analysis, we applied experiences from our previously performed “SPLIT study,” revealing that approximately 50% of people with HIV were open to splitting their STR into a two-tablet regimen [13].

Ethics

Our study obtained ethical approval from the institutional review board of the SFK, ensuring compliance with the ethical principles and general data protection regulation (GDPR) guidelines. Patient data remained confidential and were pseudonymized, upholding privacy and ethical standards.

Results

Database

Based on our inclusion criteria, we identified 1,350,514 ARV prescriptions for chronic HIV treatment in the Netherlands between 2016 and 2022. These prescriptions were linked to the total number of people with HIV, which has increased from 20,072 in 2016 to 24,573 in 2022.

Table 3 displays the fluctuations in pharmaceutical expenditure for HIV treatment during this period. Costs on antiretroviral drugs amounted to €190 million in 2016, showing a small rise to €192 million in 2017, but then demonstrated a trend of decreasing costs, ending at €180 million in 2022 (-9.4%, when compared to 2016). Notably, the cost per patient per year has declined from €9,488 in 2016 to €7,058 in 2021, with a slight increase to €7,352 in 2022 (-22.2% reduction compared to 2016).

Table 3: Number of people with HIV and expenditure (€) on antiretroviral therapy

Generic uptake trends

Table 4 contains the prescription data of single ARVs and ARV combinations that became available in generic formulations sometime between 2016 and 2022. In 2016, only 4% of prescribed DDDs were generic, primarily nevirapine (NVP). All other ARVs were not available at that time (generic ABC/3TC was introduced at the end of 2016). On average, it took approximately three years for generic formulations to obtain a substantial 90% market share, with ABC and ritonavir (RTV) being exceptions to this trend. At the end of our observation period (2022), when all analyzed ARVs had a generic formulation on the market, 97% of all the DDDs were generic. Successful uptake of generic substitutions was observed for each relevant ARV. However, it must be noted that the total number of DDDs has declined by 54.5% between 2016–2022, suggesting a switch from relatively older ARVs that now have a generic formulation.

Table 4: Distribution of generic antiretroviral drugs between 2016 and 2022

Formulations of ARVs can be divided into branded STRs (e.g., Stribild®), a branded non-STR (e.g., Truvada®), or a generic ARV (e.g., TDF/FTC, TDF/FTC/EFV, etc.). Figure 1 shows the percentage distributions of DDDs for the three ARV formulations during the study period. Branded non-STRs experienced a decline in usage from 62% in 2016 to 22% in 2022. In contrast, generic ARV formulations saw an increase in utilization from 6% in 2016 to 26% in 2022, with the highest percentage observed in 2019 at 32%. The prevalence of branded STRs also exhibits a substantial upward trend, increasing from 32% in 2016 to 52% by 2022.

Figure 1: Distribution of generics, branded MTR and branded STR between 2016 and 2022

Cost-savings

Table 5 focuses on trends in costs, prescribed DDDs, and costs per DDD for the same ARVs as in table 4, namely those where a generic formulation was introduced between 2016–2022. During this period, a decline in the costs/DDD was observed across all ARVs. The majority of ARVs that declined in costs/DDD approached 90%, except for atazanavir (ATZ), RTV, ABC, and NVP, for which fewer substantial decreases were noted.

Table 5: *Impact of generic antiretroviral drugs on costs from 2016 and 2022*

Potential cost-savings of a split strategy using generic NRTI backbones

Table 6 shows a hypothetical scenario in which a split strategy is applied to the DTG/ABC/3TC and RPV/TDF/FTC STRs using a generic NRTI backbone. The price of such a generic multi-tablet regimen (gMTR) is 30% and 60% lower than that of the branded STR. Based on the 50% acceptance we observed in our and other studies, the potential cost-savings of this strategy if it had been applied throughout the country a potential cost-savings could have been as high as €7 million per year in 2019, depending on the relative use of these combinations.

Table 6: Potential cost-savings through the splitting of single-tablet regimens between 2016 and 2022

Discussion

In summary, our study spanning 2016 to 2022 provides, valuable insights into the evolving landscape of HIV treatment in the Netherlands. Despite the increased number of people with HIV in care, pharmaceutical expenditures for HIV treatment have slightly diminished (9.4%) over time. Our data showed that the introduction of generic substitution was highly successful, contributing largely to the reduction in ART costs (22.2% lower annual ART costs per patient in 2022 vs. 2016).

In this study, we used the SFK database for the first time to provide insights into the utilization of generic ARVs and patient populations [8]. It is worth noting that, when comparing our results with those of other national databases, some differences can occur and should be explained. For instance, when examining data from the HIV Monitoring Foundation (SHM), we observed higher patient numbers (e.g., 24,381 vs. 21,397 in 2021) [1]. There could be various sources for this difference, such as potential variations in patient registration and migration patterns. These factors may include individuals who decline registration in SHM, foreign travelers/expats, Dutch citizens with HIV living abroad, and changes in the population composition due to various factors, including global events such as the conflict in Ukraine, which could have led to shifts in the demand for ART. It is important to acknowledge that these potential factors may contribute to the differences in patient numbers between databases [14]. Data from the National Institute for Public Health and the Environment (Dutch: Rijksinstituut voor Volksgezondheid en Milieu, RIVM) indicated lower HIV treatment costs, possibly because of the exclusion of certain non-reimbursed provisions [2]. By contrast, the SFK database offers a more inclusive perspective (mentioned above), capturing all prescriptions of ARVs, which may explain the difference in cost between the two sources.

Generic substitution of ARVs was highly successful, which is consistent with international observations in other cohorts. Similar studies in countries such as France, Germany, and Italy have demonstrated comparable trends, indicating the potential generalizability of our findings across certain European contexts [4, 15–17]. For instance, research conducted in Italy and France demonstrated that generic medication utilization led to significant cost savings in overall HIV expenditures [4, 15]. Germany's research has exhibited similar patterns regarding generic drug adoption and cost savings. Furthermore, they highlighted the additional cost-saving potential of splitting medication regimens, potentially reducing total expenditures by nearly 10% [17].

One of our objectives was to assess the impact of generic substitution on ARV costs. This is rather complex because many factors contribute to the overall expenditure on ARVs. For instance, we noticed large differences in costs/DDD after the introduction of a generic, ranging from 90% for TDF/FTC to 33% for ATZ. We assume that this is caused by limited competition between generic manufacturers for ATZ, whereas TDF/FTC was much more attractive for multiple generic manufacturers, probably because of its use in PrEP [18, 19]. Another confounding factor was the change in prescription patterns over time [1]. Generic ARV formulations reflect agents developed some time ago, while branded formulations often have better tolerability profiles, contain boosters less frequently, and have the advantage of low pill

burden [20, 21]. Our data reflect some of these changes in prescription patterns as the number of DDDs prescribed as generics decreased over time, from approximately 6 million DDDs of ARVs that could be prescribed as generic in 2016 to approximately 2.6 million DDDs in 2022. Consequently, cost savings by generic substitution will be less pronounced because of the transition to prescribing novel ARVs.

Nonetheless, the TDF/FTC case offers valuable insights into the impact of generic substitution on ARV costs. This combination remains a cornerstone of antiretroviral therapy, and our analysis underscores its evolution. The monthly prices for branded TDF/FTC have substantially decreased, dropping from €526 to €217. By contrast, the availability of generic TDF/FTC at a mere €28 per month contributed significantly to cost savings. In 2022 alone, with approximately 1 million DDDs of TDF/FTC dispensed, this transition resulted in a remarkable cost reduction of approximately €6.3 million, making generic TDF/FTC the largest contributor to overall expenditure reduction.

Our sub-analysis revealed a promising cost-saving opportunity through the utilization of generic multi-tablet regimens (gMTRs). For instance, in the first year of implementation in 2019, an estimated annual potential cost-saving of 7 million euros (4% of the total) could have been achieved, highlighting the substantial potential of this strategy on a national scale. These findings underscore the importance of considering this approach in cooperation with prescribers to optimize resource allocation and enhance cost-effectiveness. Policymakers and healthcare professionals can leverage these insights to maximize cost efficiency while maintaining the quality of care, benefiting both people with HIV and the broader healthcare system.

In this study, our primary focus was on interpreting the substantial cost savings achieved through the adoption of generic formulations that have progressively become more cost-effective. Notably, the cost of STRs also decreased over the study period [22, 23]. This can be attributed to the regulatory framework governing drug pricing in the Netherlands, which binds manufacturers to the maximum prices. The Dutch Medicines Prices Act (Wet GeneesmiddelenPrijzen, WGP) requires that these prices be determined based on the average prices of equivalent drugs in nearby countries. The maximum prices are reviewed biannually [24]. Recent data from the Netherlands revealed an overall decrease in the prices of medications by an average of 0.5% in April 2022 compared with the previous month [25]. However, given this modest percentage, we anticipate that the magnitude of this price reduction in medications is minimal compared with the substantial cost reductions observed in generic ARVs.

The SFK database, as disclosed in our study, is a valuable resource that complements existing data from SHM. It offers unique insights into ARV prescriptions and pharmacy dispensation, along with real-time cost data, but with a one-month delay. Future research could benefit from the capabilities of the SFK database, exploring cost-saving strategies, and resource optimization in HIV treatment. For instance, investigating the feasibility of transitioning to equally effective, yet more cost-efficient STRs would be an interesting possibility. The database's ability to monitor real-time cost data facilitates the assessment of the economic implications of such transitions and identifies areas for savings while upholding the quality

of HIV care. Our study highlights the versatility of the SFK database as a crucial tool for ongoing research aimed at enhancing the efficiency and cost-effectiveness of HIV treatment in the Netherlands.

Our study had some limitations. First, the data analyzed were specific to the Netherlands and its healthcare systems, and the findings may not be directly applicable to other regions or countries with different healthcare systems. Second, although we observed trends in the shift from branded to generic medications, the reasons behind the preferences of people with HIV and physicians for these changes have not been explored. In addition, we did not assess the clinical outcomes or side effects associated with these treatment regimens, which could have provided a more comprehensive view of their impact.

Our study has several strengths. We comprehensively examined the shift towards generic ARVs and the growing adoption of STRs in HIV treatment. Notably, we observed a substantial shift from branded to generic drugs, particularly in categories such as ABC/3TC and TDF/FTC, where generic use reached 97% in 2022. These findings highlight the cost-saving potential in HIV treatment, which can enhance healthcare economics and improve access to people with HIV. Additionally, our study revealed a substantial cost-saving strategy by opting for individual antiretroviral components over STRs, potentially resulting in substantial cost reductions, equivalent to up to 7 million euros in 2019. This study provides valuable insights into the economic considerations and cost-effectiveness of treatment choices in HIV care in the Netherlands. Although based on retrospective data, our findings are consistent with those of previous studies, emphasizing the need for further research to confirm and expand our results in a prospective context. Ongoing interventions for cost-saving and prospective research to monitor these trends are essential.Conclusion

Our six-year study highlights the substantial cost-saving potential realized through the adoption of generic antiretroviral medications, which have progressively become more cost-effective. This reduction in treatment expenditures underscores the economic benefits and cost-efficiency achieved through thoughtful treatment choices. Additionally, our findings highlight the significant cost-saving opportunities of transitioning from patented STRs to gMTRs. These outcomes underscore the importance of considering cost-saving strategies in healthcare policies to optimize resource allocation and enhance the cost-effectiveness of HIV care. Our study also introduced the SFK database as a valuable tool for real-time cost data and research opportunities in HIV treatment optimization.

Abbreviations

3TC
Lamivudine
ABC
Abacavir
ABC/3TC
Abacavir/Lamivudine
ART

Antiretroviral Therapy
ARVs
Antiretrovirals
ATC
Anatomical Therapeutic Chemical
ATZ
Atazanavir
DDD
Defined Daily Dose
DTG
Dolutegravir
EFV
Efavirenz
GDPR
General Data Protection Regulation
gMTR
Generic Multi–Tablet Regimen
HIV
Human Immunodeficiency Virus
NRTI
Nucleoside Reverse Transcriptase Inhibitors
NVP
Nevirapine
PEP
Post–Exposure Prophylaxis
PrEP
Pre–Exposure Prophylaxis
RPV
Rilpivirine
RTV
Ritonavir
SFK
Stichting Farmaceutische Kengetallen (Foundation for Pharmaceutical Statistics)
SHM
HIV Monitoring Foundation
STR
Single–Tablet Regimen
TAF
Tenofovir Alafenamide Fumarate
TDF

Tenofovir Disoproxil Fumarate
TDF/FTC
Tenofovir Disoproxil Fumarate/Emtricitabine
WGP
Wet GeneesmiddelenPrijzen (Dutch Medicines Prices Act

Declarations

Ethics approval and consent to participate

Not applicable. This study utilized an existing database (Foundation for Pharmaceutical Statistics - SFK) in the Netherlands which aggregates anonymized pharmacy data for research purposes. As such, individual patient consent was not required and the study did not involve direct participation. The use of this database for research has been approved by the SFK committee, ensuring compliance with national guidelines for data privacy and ethical research conduct (Foundation for Pharmaceutical Statistics — SFK Website).

Consent for publication

Not applicable.

Availability of data and materials

The dataset analyzed in this study is not publicly available but can be made available upon reasonable request by the Foundation for Pharmaceutical Statistics (SFK) and Piter Oosterhof.

Competing interests

PO received personal consulting fees from ViiV healthcare, Gilead, and Merck Sharp & Dohme. KB received personal consultation fees from Merck, Gilead, and ViiV. KB has received a writing honorarium from UpToDate. The remaining authors have no conflicts of interest to declare.

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Authors' contributions

PO, DB, MVL and KB contributed to the conceptualization and design of the study. PO and DB designed the methods of the study. PO performed data analysis and wrote the original draft of the manuscript, including the figures. JWV advised on data cleaning and served as an additional check for the associated SPSS syntax. All co-authors (JWV, MVL, KB and DB) had full access to all data in the study and had final responsibility for the decision to submit for publication.

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Tables

Table 1 to 6 are available in the Supplementary Files section.

Figures

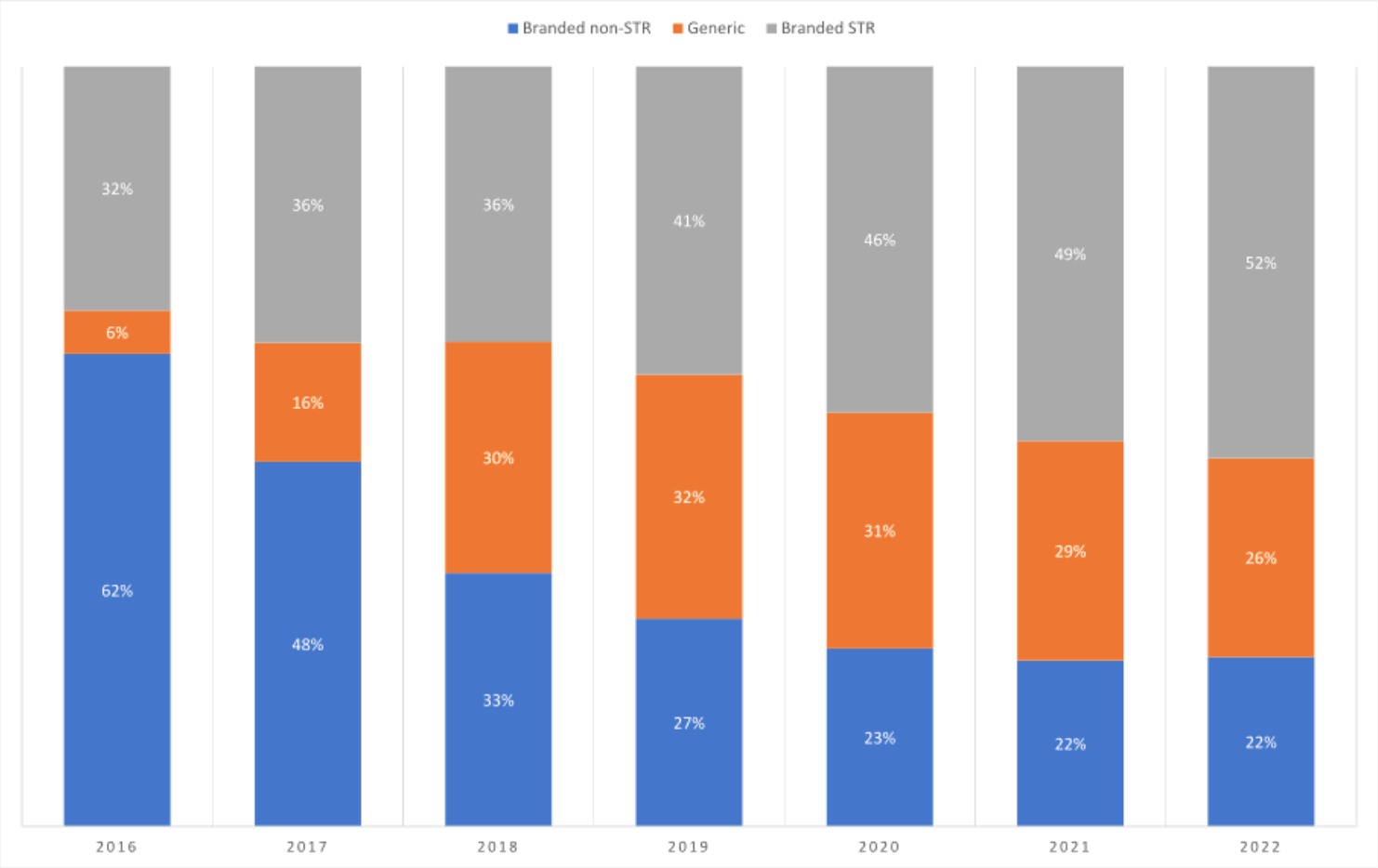

Figure 1

Distribution of generics, branded MTR and branded STR between 2016 and 2022

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- Table2.docx
- Table3.docx
- Table4.docx
- Table5.docx
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