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Universidade Nova de Lisboa
Instituto de Higiene e Medicina Tropical

Hospital Quality Measures and their Determinants among
HIV/AIDS Hospitalizations in Portugal

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**DISSERTAÇÃO PARA A OBTENÇÃO DO GRAU DE DOUTOR EM SAÚDE PÚBLICA
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“Really the whole hospital problem rests on one question: What happens to the cases? [. . .]

We must formulate some method of hospital report showing as nearly as possible what are the results of the treatment obtained at different institutions. This report must be made out and published by each hospital in a uniform manner, so that comparison will be possible.

With such a report as a starting-point, those interested can begin to ask questions as to management and efficiency.” (Dr Eugene Codman, 1913)

A minha mais sincera gratidão...

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Abstract

Thirty-day readmission rate, and length of hospital stay have drawn attention as methods for enhancing the quality of care and reducing associated costs. However, despite being optimal methods for assessing hospital's performance, there remains a scarcity of research pertaining to the factors that can influence these quality indicators, especially when it comes to assessing hospitalizations among HIV/AIDS patients in Portugal. In Portugal, HIV continues to be a major public health concern and HIV incidence and prevalence are among the highest in Europe. Admissions among HIV/AIDS patients still pose considerable challenges to the Portuguese national health system. Moreover, hospitalizations related to HIV/AIDS in Portugal are some of the most expensive, placing HIV/AIDS as the second greatest Major Diagnostic Category.

This thesis aims to assess hospital quality measures and their determinants among HIV/AIDS hospitalizations in Portuguese public hospitals. The work also aims to identify variation in thirty-day readmission rate and length of stay among HIV/AIDS admission in public Portuguese hospitals. To accomplish these objectives, four studies (I – IV) were performed using data obtained from the Portuguese Central Health System Administration (ACSS), and following different designs. Studies I reviewed the economic burden of hospitalizations among HIV/AIDS hospitalizations in Portugal, explaining the importance of implementing quality indicators to measure the performance of hospitals, as well as possible ways to study the factors that can affect these quality indicators. Study II emphasized the crucial role quality measures can play in mitigating the financial burden imposed by the novel coronavirus disease (COVID-19) pandemic on the health system. A longitudinal multilevel population-based study was conducted in study III to estimate the 30-day hospital readmission rates among HIV hospitalizations in Portugal. Moreover, this study aimed to describe and analyze factors associated with subsequent 30-day readmission among HIV patients in Portugal by applying ordinary and multilevel logistic regression models. In study IV, a count regression analysis using a random-effects model was conducted to illustrate statistical techniques for analysing count data using longitudinal predictors of length of stay among HIV hospitalizations in Portugal. Several strategies were applied to select the best count fit model including the Poisson regression model, the zero-inflated Poisson, the negative binomial regression model, and the zero-inflated negative binomial regression model. A random hospital effects term was

incorporated into the negative binomial model to examine the dependence between observations within the same hospital. A multivariable analysis was performed to assess the effect of covariates on length of stay.

A total of 4914 [13.2%, 95% confidence interval (CI): 12.9%–13.6%] hospitalizations had a subsequent 30-day readmission. Hospitalizations that included discharge against medical advice [odds ratio (OR) = 1.18, 95% CI: 1.01–1.39], scheduled admissions (OR = 1.71, 95% CI: 1.58–1.85), and tuberculosis infection (OR = 1.20, 95% CI: 1.05–1.38) exhibited a higher odds of hospitalizations with subsequent 30-day readmission. In contrast, hospitalizations among females (OR = 0.87, 95% CI: 0.81–0.94), that included a transfer to another facility (OR = 0.78, 95% CI: 0.67–0.91) and having a responsible financial institution (OR = 0.63, 95% CI: 0.55–0.72) exhibited a lower odds of hospitalizations with subsequent 30-day readmission. Hospitalizations associated with a higher number of diagnoses, older ages, or hospitalizations during the economic crisis showed an increasing trend of 30-day readmission, whereas an opposite trend was observed for hospitalizations with a higher number of procedures. Significant differences exist between hospital quality, even after adjusting for other factors.

The median length of stay in the study was 11 days (interquartile range: 6–22). Statistical comparisons across the count models revealed that the random-effects negative binomial models provided the best fit with observed data. Admissions among males, or admissions associated with tuberculosis infection, pneumocystis, cytomegalovirus, candidiasis, toxoplasmosis or mycobacterium disease exhibit a high significant increase in length of stay. Perfect trends were observed in which a higher number of diagnoses or procedures lead to a significantly longer length of stay. The random-effects term included in the model refers to unexplained factors specific to each hospital and revealed obvious differences in quality across the hospitals included in the study.

This thesis contributes to attempts to reduce the economic burden of HIV/AIDS in Portugal and point to the importance of integrating quality measures such as a method for evaluating the performance of hospitals in light of limited resources. Findings from this thesis are supported by a large database that represents all Portuguese public HIV/AIDS admissions and can help develop a national health policy to avoid unnecessary readmissions or delayed discharges. These findings can also set the basis for new insights that can focus on patients at

high risk of early readmission or prolonged length of stay. The models and statistical frameworks described in this thesis can be replicated and applied to other diseases and settings.

Resumo

A taxa de reinternamento hospitalar aos 30 dias e o tempo de internamento hospitalar têm sido referidos como importantes indicadores para melhorar a qualidade e reduzir os custos hospitalares. No entanto, apesar de se tratarem de excelentes métodos de avaliação de desempenho hospitalar, ainda existem poucos estudos científicos sobre os fatores determinantes destes indicadores, especialmente no que diz respeito à avaliação de internamentos em doentes com VIH/SIDA em Portugal. O VIH continua a ser, em Portugal, um e problema de saúde pública e a incidência e prevalência do VIH estão entre as mais elevadas da Europa. Os internamentos de doentes com VIH/SIDA continuam a colocar desafios consideráveis ao sistema nacional de saúde português. Acresce que as hospitalizações relacionadas com o VIH/SIDA em Portugal são das mais caras da Europa, colocando o VIH/SIDA como a segunda maior Categoria de Diagnóstico Principal.

Esta tese tem como objetivo analisar medidas de qualidade hospitalar e seus determinantes nos internamentos por VIH/SIDA em hospitais públicos portugueses (Portugal Continental). Mais especificamente, estimar a taxa de reinternamento aos 30 dias e do tempo de internamento por VIH/SIDA ao longo do tempo e fatores associados. Para cumprir estes objetivos, foram realizados quatro estudos (I - IV) com dados obtidos junto da Administração do Sistema Central de Saúde (ACSS) de Portugal, e seguindo diferentes desenhos. O Estudo I faz uma revisão da carga económica dos internamentos considerando as hospitalizações por VIH/SIDA em Portugal, explicando a importância da implementação de indicadores de qualidade para medir o desempenho dos hospitais, bem como possíveis formas de estudar os fatores que podem afetar esses indicadores de qualidade. O Estudo II enfatizou o papel crucial que as medidas de qualidade podem desempenhar na mitigação dos encargos financeiros impostos pela nova pandemia de doença do coronavírus (COVID-19) no sistema de saúde. Um estudo longitudinal multinível de base populacional foi conduzido no estudo III para estimar as taxas de reinternamento hospitalar aos 30 dias nas hospitalizações por VIH em Portugal. Além disso, este estudo teve como objetivo descrever e analisar os fatores associados aos reinternamentos aos 30 dias em doentes com VIH em Portugal, através da aplicação de modelos de regressão logística ordinária e multinível.

No estudo IV, foi realizada uma análise de regressão de contagem com efeitos aleatórios para ilustrar técnicas estatísticas úteis na análise de dados de contagem usando dados

longitudinais do tempo de internamento em hospitalizações por VIH em Portugal. Várias estratégias foram aplicadas para selecionar o modelo que melhor se ajustava, incluindo o modelo de regressão de Poisson, o modelo de regressão binomial negativo inflacionado, o modelo de regressão binomial negativo e o modelo de regressão binomial negativo inflacionado de zero. Um termo de efeitos aleatórios foi incorporado ao modelo binomial negativo para examinar a dependência entre as observações dentro do mesmo hospital. Uma análise multinível foi realizada para avaliar o efeito das co variáveis no tempo de internamento.

Os reinternamentos aos 30 dias totalizaram 4914 hospitalizações [13,2%, intervalo de confiança de 95% (IC): 12,9% –13,6%]. Internamentos que incluíram alta contra orientação médica [odds ratio (OR) = 1,18, IC 95%: 1,01-1,39], admissões programadas (OR = 1,71, IC 95%: 1,58-1,85) e infeção por tuberculose (OR = 1,20, 95 % CI: 1,05-1,38) tiveram uma maior chance de reinternamento aos 30 dias. Em contraste, as hospitalizações entre mulheres (OR = 0,87, IC 95%: 0,81–0,94), que incluíram uma transferência para outra unidade (OR = 0,78, IC 95%: 0,67–0,91) e ter uma instituição financeira responsável (OR = 0,63 , 95% CI: 0,55-0,72) tiveram uma menor chance de reinternamento aos 30 dias. Os internamentos associados a maior número de diagnósticos, idade avançada ou internamentos durante o período de crise económica tiveram um efeito positivo na probabilidade de reinternamento aos 30 dias, enquanto que tendência oposta foi observada para internamentos com maior número de procedimentos. Existem diferenças significativas entre a qualidade dos diferentes hospitais, mesmo ajustando para outros fatores.

O tempo mediano de internamento hospitalar foi de 11 dias (intervalo interquartil: 6-22). As comparações entre os diversos modelos de contagem sugerem que os modelos binomiais negativos com efeitos aleatórios forneceram o melhor ajuste os dados observados. As admissões entre homens ou associadas à infeção por tuberculose, pneumocisto, citomegalovírus, candidíase, toxoplasmose ou doença por micobactéria aumentam significativamente o tempo de internamento estimado. Estimou-se igualmente que um maior número de diagnósticos ou procedimentos está relacionado com um tempo de internamento significativamente maior.

A estimação dos efeitos aleatórios para cada hospital revelou diferenças na qualidade entre os hospitais incluídos no estudo, mesmo ajustando aos outros fatores.

Esta tese contribuiu para o aprofundamento dos fatores relacionados com a carga económica do VIH/SIDA em Portugal. As conclusões sugerem a importância de integrar medidas de qualidade, baseadas no tempo de internamento hospitalar e taxa de reinternamento como um método de avaliação do desempenho dos hospitais, nomeadamente num contexto de recursos escassos. Os resultados desta tese são suportados por uma grande base de dados que representa todas os internamentos nos hospitais públicos de Portugal Continental por VIH/SIDA; estes achados também podem ajudar a definir a base para novas abordagens que tenham em linha de conta pacientes com alto risco de reinternamento precoce ou tempo de internamento prolongado. Os modelos e especificações estatísticas descritas nesta tese podem ser replicados e aplicados a outras doenças e contextos.

Background

Introduction

Hospital outcome measures for quality of care

Hospitals represent a fundamental and vital element of the health system. However, hospitals are also considered the most expensive element and represent a heavy burden to health systems worldwide. A large portion of total inpatient costs is linked to the consumption of resources that include medications, diagnostics, procedures and expenses correlated with resources associated with inpatient stay, such as hospital infrastructure, operation costs and human resources. In the United States (US), hospitalizations account for nearly 50% of the total healthcare expenditure (1, 2). In Europe, total spending on hospital admissions is showing an increasingly positive trend as hospital expenditure represents roughly 38.2% of the total healthcare expenditure (3). Hospital expenditure in Portugal is classified among the highest in the EU as it accounts for 42% of the total health expenditure (3). However, evidence suggests that resources utilized in hospitals can be redirected to more efficient utilization, as several countries demonstrated that 20% of health expenditure, including inpatient care, was wasteful or unnecessary (4). For example, potentially avoidable or preventable hospital admissions consume around 37 million bed days annually in the EU and can be interpreted as deficiencies in managing health problems in other inexpensive settings (4). Moreover, unnecessarily delayed discharges, which contribute to longer hospital stays and more operational costs, could add further economic pressure to the health system (4). Accordingly, addressing factors that can increase length of stay (LOS) could save hospital resources or resources for new admissions with greater needs.

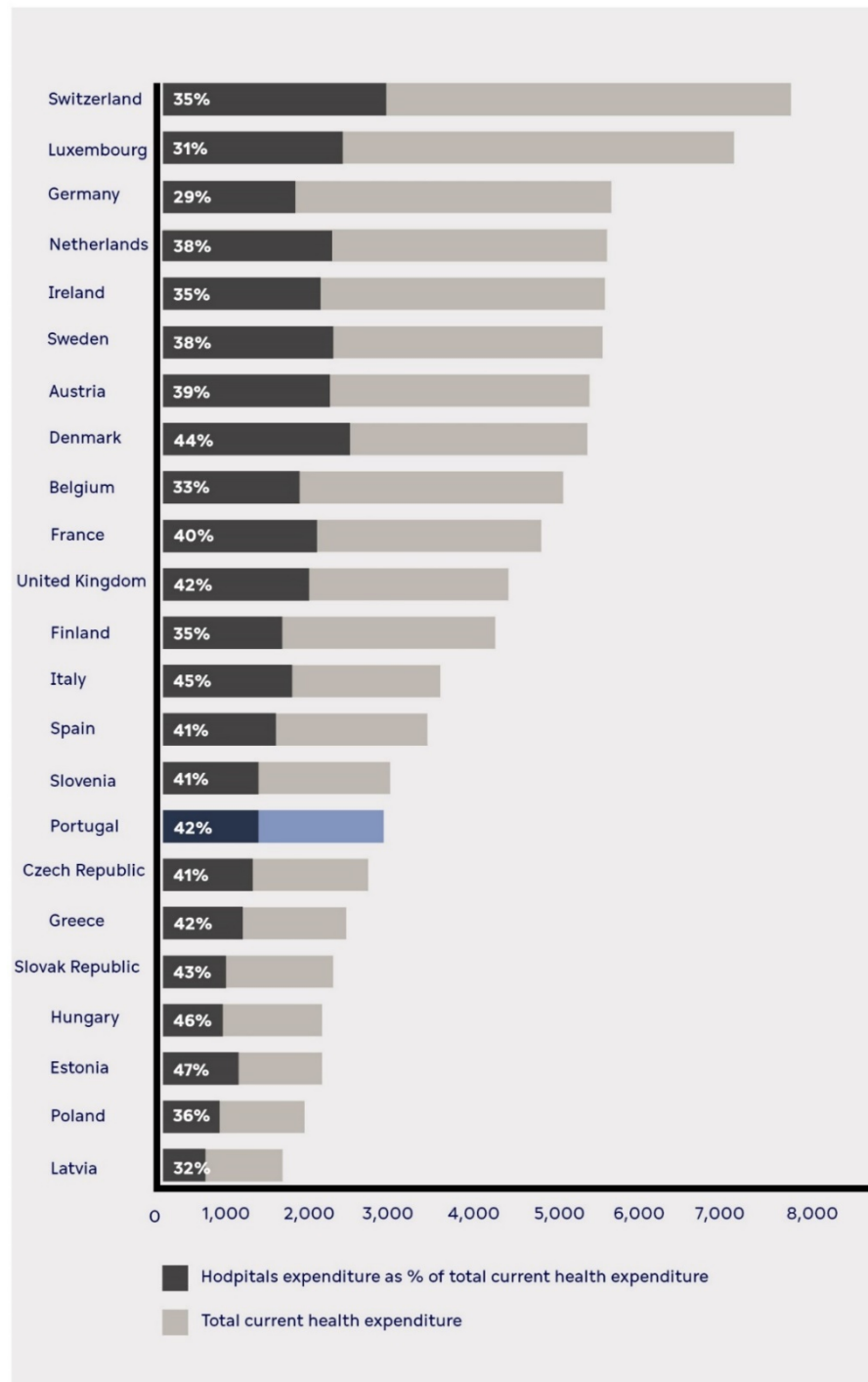


Figure 1. Hospital expenditure as percentage of total current health expenditure in Europe.
Source: Hospital Healthcare Europe: Hospitals in Europe: Healthcare data (3).

These facts highlight the importance of decreasing unnecessary spending by focusing on particular areas of improvement through measuring and monitoring the performance of hospitals. Outcome measures for quality of care have been frequently adopted as a way to control and compare hospital performance, with a goal of identifying areas for improvement (5). Evidence suggests that adopting these quality indicators to measure hospital performance could save millions in preventable admissions and bed days in Europe (4). In this sense, comparable and comprehensive assessments of hospital quality indicators can control health expenditure by identifying significant gaps in spending and assessing the allocation of resources (6). Accordingly, it is crucial to set benchmarks that allow for comparisons between different hospitals and use the results of these comparisons to enhance the quality of care (4). Benchmarking is a process that allows for a comparison to be made to other organizations by establishing a standard of quality and uses these comparisons to make improvements. For example, the US Centers for Medicare and Medicaid Services (CMS) use these benchmarks to determine how well a hospital performs and, accordingly, determine hospital reimbursement rates (4). Recent quality indicators that are gaining growing attention as measures to evaluate the quality of care of hospitals are 30-day readmission and LOS (5, 7). The creation and implementation of these measures are of paramount importance given their role in evaluating the quality of healthcare, and detecting and highlighting possible areas for improvement (8). Moreover, several schemes have been established to incentivize or penalize hospitals according to these quality measures (9-11). Examples of these schemes are pay for performance (P4P) (8) and Pay for Quality (P4Q) (12) that have been adopted in several healthcare contexts. These schemes are attributed to financial incentives paid to a healthcare provider for accomplishing a quality-related target within a defined timeline (13). According to these schemes, hospitals can be rewarded or penalized based on different aspects, including structures, processes or quality outcomes (13, 14). In this sense, hospitals are required to plan and implement actions to enhance the quality of care and reduce associated costs (15). Therefore, hospitals are required to develop and distribute information regarding hospital quality indicators with several entities, such as health authorities and health insurance companies (15).

The World Health Organization (WHO) stressed the importance of using and understanding these indicators to guide policymaking and management, particularly in countries with public funding challenges (16). However, in many countries, data regarding these indicators or analytical techniques are not fit for purpose (16). The lack of such measures may mislead the decisions of policymakers by adopting crude cost reduction policies that haphazardly impact both inefficient and efficient health institutions and professionals (16).

Valid and precise quality measurement, and a proper interpretation of factors that can affect these indicators are necessary for issuing focused and practical strategies towards improving quality (16). However, despite this, measuring and monitoring hospital performance and quality of care are complex and challenging. Creating and implementing these indicators should consider their nature and their statistical aspects. Nevertheless, the development of fairly recent statistical methods, such as count regression models and random-effects models, has allowed for complex data to be analyzed.

Thirty-day readmission

Thirty-day hospital readmission is defined as an episode in which a patient is readmitted within 30 days from the last discharge (17). Most avoidable readmissions have been documented to occur within 30 days of the last discharge, and this time frame has been normally adopted in comparative studies (18-20). The operational indicator for 30-day hospital readmission is the 30-day readmission rate, which is the percent of 30-day readmissions out of the total admissions. Early or premature readmissions have been frequently used as a quality indicator to measure hospital performance and as a quality benchmark for health systems (21-23). Besides its role as a quality indicator, 30-day hospital readmissions have also been praised as a way to control healthcare spending, as they are known to be associated with adverse outcomes and high economic burden (9, 24). In the last few decades, early hospital readmissions were the focus of retrospective studies and prospective trials aiming at their prevention (1). Accordingly, assessing the frequency of readmissions and, most importantly, their causes are of paramount importance.

Although early readmissions could be avoided in most cases, they have been identified as frequent and costly, making them a target for cost reduction, and identifying them is a national priority for several countries (24-27). For example, in the US, nearly 13% of the inpatient admissions utilize nearly 50% of all hospital resources through readmissions (2). Moreover, one-fifth of Medicare recipients have a 30-day readmission, with an annual cost of around \$26 billion (24, 27). The Medicare Payment Advisory Commission (MedPAC) has estimated that preventing 10% of these readmissions could save Medicare \$1 billion (28). Considering this, in 2008, MedPAC suggested that CMS should establish communicating early readmission rates and their cost (29). Following this recommendation, the CMS started communicating readmission rates for included hospitals (9). Accordingly, policy proposals

recommended creating incentives and reimbursements to decrease the rates of premature readmissions. Thus, hospitals with high rates of early readmissions would receive lower average payments per case (24). In this context, several programs have been implemented to incentivize or penalize hospitals according to their readmission rate. For example, the American Affordable Care Act (ACA) implemented the Hospital Readmission Reduction Program (HRRP) in 2012, in which institutions are awarded or penalized according to their 30-day readmission rates (9). Moreover, the American National Quality Forum was approved using the readmissions rate as a way to determine hospital reimbursement (30, 31). Additionally, controlling unnecessary readmissions was also an essential component of the political leadership scheme for financing healthcare reform, in which there is a fundamental change in the responsibility of hospitals regarding patient outcomes after discharge (24, 32).

Several studies have emphasized the importance of assessing factors that may contribute to 30-day readmission as a crucial step toward addressing any irregularities. Of particular importance, the causes of 30-day readmission are multifactorial, and readmission rates vary substantially by institution (9, 33, 34). For example, poor quality of care during admission, poor case management at discharge or follow-up increase the risk of subsequent readmissions, as shown in several studies (35, 36). These poor quality aspects include inefficient resolution of the primary problem, inadequate treatment at discharge or incompetent care following discharge. Previous studies also found that readmission rate differed according to socioeconomic or sociodemographic factors, such as gender (37, 38), age (39), marital status (40), socioeconomic status (41-43), race (37), insurance coverage (37) and geographic variability (1). Other studies found that clinical factors, such as illness severity (44), comorbidity (38), diagnosis (41, 45-49), psychiatric disorders (50), behavioral disorders (41) and nutritional status (14, 51, 52), contribute significantly to readmission rates. Additionally, LOS during hospitalization (37, 38, 53), discharge destination (1) and previous use of hospital resources (39) were identified as important predictors of 30-day readmission. It is important to mention that a considerable number of readmissions are attributed to avoidable causes (1). Avoidable readmissions in previous studies have been estimated to be as low as 9% and as high as 55%, with some studies reporting 20%, 21% and 23% (35, 54-57). These studies found that these avoidable readmissions could be attributed to low quality, improper care and modifiable factors during or following hospitalization. Evidence also suggested that the rate of readmissions can be reduced through several interventions. Previous research has shown that specific measures at the time of discharge can significantly decrease readmission rates (58-60). Patient education, predischarge evaluation and at home aftercare can reduce readmissions by

between 12% and 75% as shown in previous randomized trials (1). Moreover, the application of pre-discharge and follow-up plans have been shown to decrease readmission rates (61-63).

Length of stay

LOS is defined as the total number of days a patient spent during inpatient admission. The operational indicator for this quality indicator is the average LOS calculated by dividing the total number of inpatient days for all patients by the number of patients admitted to a particular hospital (64). LOS has been used as an indicator to assess the effectiveness of preventive, diagnostic and therapeutic schemes, clinical pathways, and consumption of hospital resources (65, 66). However, LOS is also thought to be a major quality indicator and has been frequently used as a benchmark to compare the performance of hospitals (66). Oftentimes, LOS is categorized by the diagnosis of each patient to compare the LOS with other organizations (14). Since inpatient care is significantly expensive compared with alternative settings, patients who are well enough to leave the hospital should be discharged or continue care in an alternative, less costly setting, hence, reducing inpatient LOS (4, 64, 67). It is also important to mention that longer LOS can be interpreted as an indicator of poor quality and more consumption of hospital resources (4, 64). Prolonged stays contribute to growth in hospitals and health system expenses due to unnecessary hospital bed utilization, in which care may be better offered through alternative settings, such as home or long-term care (68-70). It is well established that extended LOS consumes considerable hospital resources, and hence, decreasing LOS will result in more efficient and effective care (71). LOS is an essential indicator of resource consumption as admissions with delayed discharges are linked to an unnecessary utilization of resources, affecting both hospitals and patients in different ways (72, 73). Moreover, exceeding the expected duration for a specific diagnosis or procedure, hence unnecessarily utilizing hospital beds and causing hospital capacity shortage (74). This capacity shortage will delay new admissions and deny other patients timely access to treatment (75, 76). Additionally, patients with prolonged LOS are at higher risks of nosocomial infections during hospitalization and unnecessary readmissions (77-79).

As for early readmissions, several programs have created incentives to decrease LOS (71, 80, 81). Entities such as the CMS and health insurers have called for using LOS as a crucial indicator for the quality of care in which reimbursement rates should be determined according to LOS (81). Moreover, the University Health System Consortium, the National Trauma Data Bank and the National Surgical Quality Improvement Program recommended LOS reduction as a way for efficient care since prolonged LOS usually consumes substantial resources (71).

From this perspective, these entities created a regular reporting system in which LOS data indexed to benchmark are distributed among the included hospitals, enabling comparisons between hospitals (71). Additionally, many European countries observe LOS and create financial incentives for reducing unnecessary delayed discharges (4). For example, several Nordic countries apply penalties on hospitals with unnecessary prolonged stays, which led to a marked decrease in LOS (4). As an illustration, the significant growth in this applied financial penalty in Denmark ranges from €530 to €795 per day, which resulted in a sharp decrease in LOS. Additionally, other countries, such as Norway start planning discharges as early as the patient is admitted to the hospital, which aims to decrease LOS (4).

Similar to early readmissions, several factors can contribute to prolonged LOS, such as patient-related characteristics, socioeconomic and demographic factors, clinical factors, a variation in services provided by different hospitals, and poor transition planning and care coordination (71, 82-89). For example, on the patient and clinical levels, factors such as age, gender, insurance or payer status, functional status, diagnostic or comorbidity factors are found to contribute to prolonged LOS (71, 74, 75, 90-95). On the organizational level, factors related to the administrative elements of hospitals, such as delayed examinations, procedures and discharge planning, have been documented as predictors of prolonged LOS (75, 79, 96). Identifying risk factors for prolonged LOS provides insights into possible strategies to decrease LOS, since hospitals can tackle modifiable risk factors with this knowledge (97).

As for the rest of the world, prolonged LOS in the EU is attributed to several social, health and organizational factors (4). However, although the average inpatient LOS has declined in almost all EU countries between 2000-2016, LOS did not show a significant decline in Portugal during the same period (Figure 2) (98).

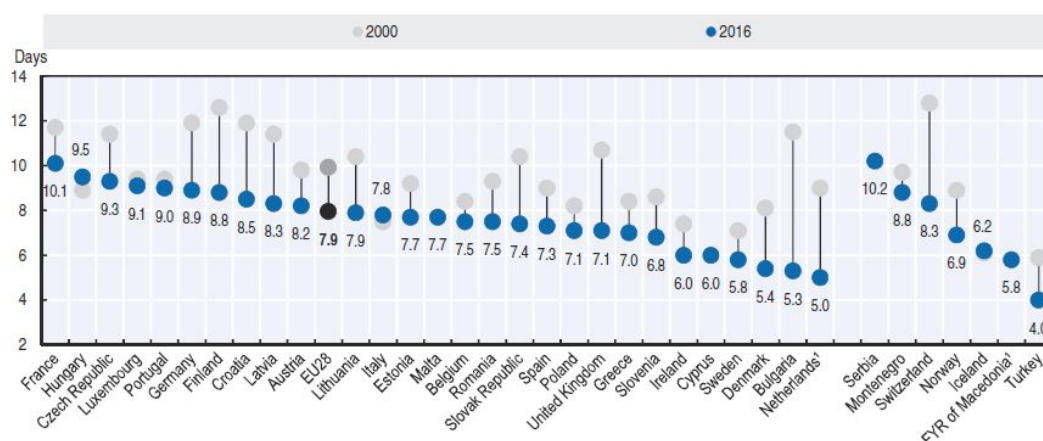


Figure 2. Average LOS in hospital, 2000 and 2016 (or nearest year).

LOS: Length of Stay.

Source: Health at a Glance: Europe 2018 (98).

This work aims to study healthcare quality indicators among hospital admissions related to the human immunodeficiency virus (HIV) or the acquired immunodeficiency syndrome (AIDS) in Portugal. Health expenses related to inpatient care of People Living With HIV/AIDS (PLWHA) remain comparatively costly and resource-intensive since it is assigned to cure serious related admissions (99-104). However, despite this burden and the high prevalence and incidence of HIV/AIDS in Portugal, there is limited research regarding the factors that can contribute to early readmissions and prolonged LOS among HIV/AIDS patients at a national level. Therefore, better monitoring of prolonged hospital stays and early readmissions, and their determinants are crucial for developing more customized measures based on assessing the possible risk factors. Additionally, defining the possible factors that can push these measures further may improve discharge planning and establish effective strategies to decrease LOS and early readmissions among HIV/AIDS patients.

Historical overview of the human immunodeficiency virus

Human immunodeficiency virus

HIV is an enveloped retrovirus, classified as the genus *Lentivirus* inside the family of *Retroviridae*, subfamily *Orthoretrovirinae* (105). The virus targets and replicates inside CD4 cells, a critical cell in responding to infections and producing a regulated effective immune response to pathogens (106). Over time, the CD4 cells count declines, and decreases the body's capacity to recognize and combat infections. Without treatment, the virus weakens the host's immune system leading to opportunistic infections, AIDS and death. The virus contains two copies of a single-stranded ribonucleic acid (RNA) genome (105). Shortly after the HIV capsid enters the host cell, the virus, through its reverse transcriptase enzyme, starts to convert the RNA into proviral deoxyribonucleic acid (DNA) (107). Later, HIV uses another enzyme, HIV's integrase enzyme, to integrate the DNA into the genome, and hence, starts virus replication (108). These two steps are the main features of the *Retroviridae* and are essential steps in retroviral replication (107).

HIV can be transmitted through several modes that include sexual intercourse, injured skin or mucosa, infected needles, blood transfusion, mother-to-child transmission and breastfeeding (109-115). However, the majority of HIV infections occur through sexual transmission (114, 115). Within around two weeks of infection, the virus can be found in the entire body (105). Regarding variations in genetic features, the virus is classified into type 1 and type 2 (HIV-1 and HIV-2, respectively) (105). HIV-1 is the most prevalent type globally, and HIV-2 is relatively limited to West Africa and to a much-limited degree to Europe, with respect to Portugal and France (116-118). HIV-1 can be grouped into four groups: M, N, O and P (Figure 3), with Group M being the most common worldwide (119). Moreover, Group M can be categorized into nine subgroups A, B, C, D, F, G, H, J and K, and hybrid combinations of subgroups referred to as circulating recombinant forms (CRFs) (Figure 3) (119). CRFs are defined as the outcome of viral reproduction inside the host infected cell with two subgroups. The distribution of virus subgroups is patterned and shaped by geographical regions and risk groups. However, these patterns have been recently diluted due to frequent migrations and sexual behaviors (120). In Portugal, as a part of Western Europe, the predominant type is HIV-1, Group M (121). The B subgroup continues to be the most prevalent subgroup in Portugal and Western Europe (120, 121). However, the spread of non-B subgroups is increasing in

Western Europe, with Portugal being the country with the greatest HIV-1 subgroups heterogeneity (120, 122-127). In contrast to the West of Europe, Portugal has higher rates of the G subgroup (120, 128-133). These elevated rates of B and G subgroups in Portugal are believed to have developed during the 1990s. Afterward, they have been transmitted to the other European States through intravenous drug users (IDU) (120).

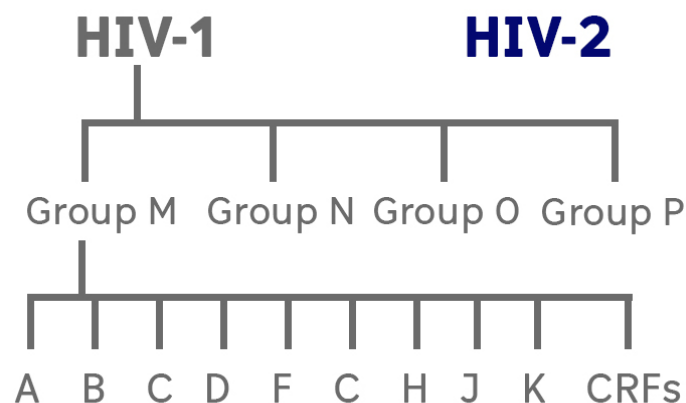


Figure 3. HIV types and strains.

CRFs: Circulating Recombinant Forms; HIV: Human Immunodeficiency Virus.

Adopted from Avert | Global information and education on HIV and AIDS (134).

The rates of HIV-2 are elevated in some European States that are known to have historical old ties and connections with African regions, particularly France and Portugal (135-137). HIV-2 infection is thought to have originated from previous Portuguese and French African colonies, from where HIV-2 has spread to Europe (138, 139). Portugal remains the European country with the highest prevalence of HIV-2 infection (136, 137, 139, 140). The first case of HIV-2 was reported in a Portuguese hospital (Egas Moniz, Lisbon) in 1987 in a patient from Guinea-Bissau (139, 141). All evidence indicates that Guinea-Bissau, a former Portuguese colony, is the original geographical heartland of HIV-2 infection, namely, a small region located near Canchungo Medical Centre in North-Western Guinea-Bissau (118, 135). The transmission of HIV-2 infection appears to have happened after 1960-1970, although previous studies suggest that the spread of HIV-2 may have occurred between 1924 a 1956 (118, 135, 142). The Portuguese colonial war that started in 1961 helped spread HIV-2 infection in this African country through sexual transmission and blood transfusion due to war injuries (118, 135, 139, 142). After the colonial war ended in 1974, the return of the Portuguese

soldiers helped spread HIV-2 in the Portuguese mainland. Moreover, the political instability in Guinea-Bissau during the late 1990s that led to a migration wave from Guinea-Bissau to Portugal later contributed to the high rates of HIV-2 in the early 2000s (135, 143).

The lifecycle of HIV

Understanding the lifecycle of HIV was a crucial step to examine molecules that would prevent its reproduction and allowed the production of antiretroviral medications aimed to block essential steps of this lifecycle. The HIV genome includes several genes, encoding proteins and mandatory enzymes for its reproduction (Figure 4) (144-146). The first step in the HIV lifecycle is when the virus binds to the CD4 receptors through the viral glycoprotein 120 (gp120), which later facilitates binding to the CCR5 or CXCR4 chemokine coreceptor, known as X4 and R5, respectively (144, 147-151). The CD4 receptor is present on the surface of several cells, such as macrophages, monocytes, T lymphocytes and dendritic cells (152). This step allows glycoprotein 41 (gp41) also known as fusion peptide, to break through the host's cell membrane and allows HIV to translocate its genetic material (RNA) into the cytoplasm (153).

After the RNA enters the host cell cytoplasm, the RT enzyme transcribes RNA into a complementary DNA (cDNA) copy (Figure 4) (105, 154). This critical phase of replication is highly subjected to errors due to the deficiency of the proof-reading capacity of the enzyme. Any changes during this phase could cause resistance to antiretroviral drugs or enable the virus to avert the immune system (155-158). Moreover, the RT enzyme, through its DNA-dependent polymerase activity, transforms cDNA into double-stranded DNA known as proviral DNA (159). Afterward, the proviral DNA is transported to the nucleus of the host cell (105).

The third step occurs when the virus integrates the proviral DNA into the cell genome through its viral integrase enzyme (144, 160, 161). This integration step results in persistent infection (105). The integrated proviral DNA may remain in a latency phase for years (162). The virus's active reproduction demands particular transcription factors, most notably the NF kappa B (NF- κ B) (163, 164). An infected cell's activation will trigger the integrated proviral DNA to produce the messenger RNA (mRNA) through an RNA polymerase. Later, the mRNA moves towards the cell's cytoplasm and transforms into immature viral proteins (144).

The viral protease cleaves the long chain polyproteins into smaller polypeptides (165, 166), which then cluster with other genetic material to generate a new virus particle. Finally,

the virus buds through the cell membrane, which acts as an envelope for the viral genetic material and at the same time carries the viral glycoproteins (gp120 and gp41) over its surface (167). These viral glycoproteins will again bind to CD4 receptors to restart the virus's life cycle. The estimated *in vivo* HIV-1 lifecycle is 1.2 days (168). However, the period from the discharge of a virion to infect another cell and produce another viral particle is 2.6 days (168).

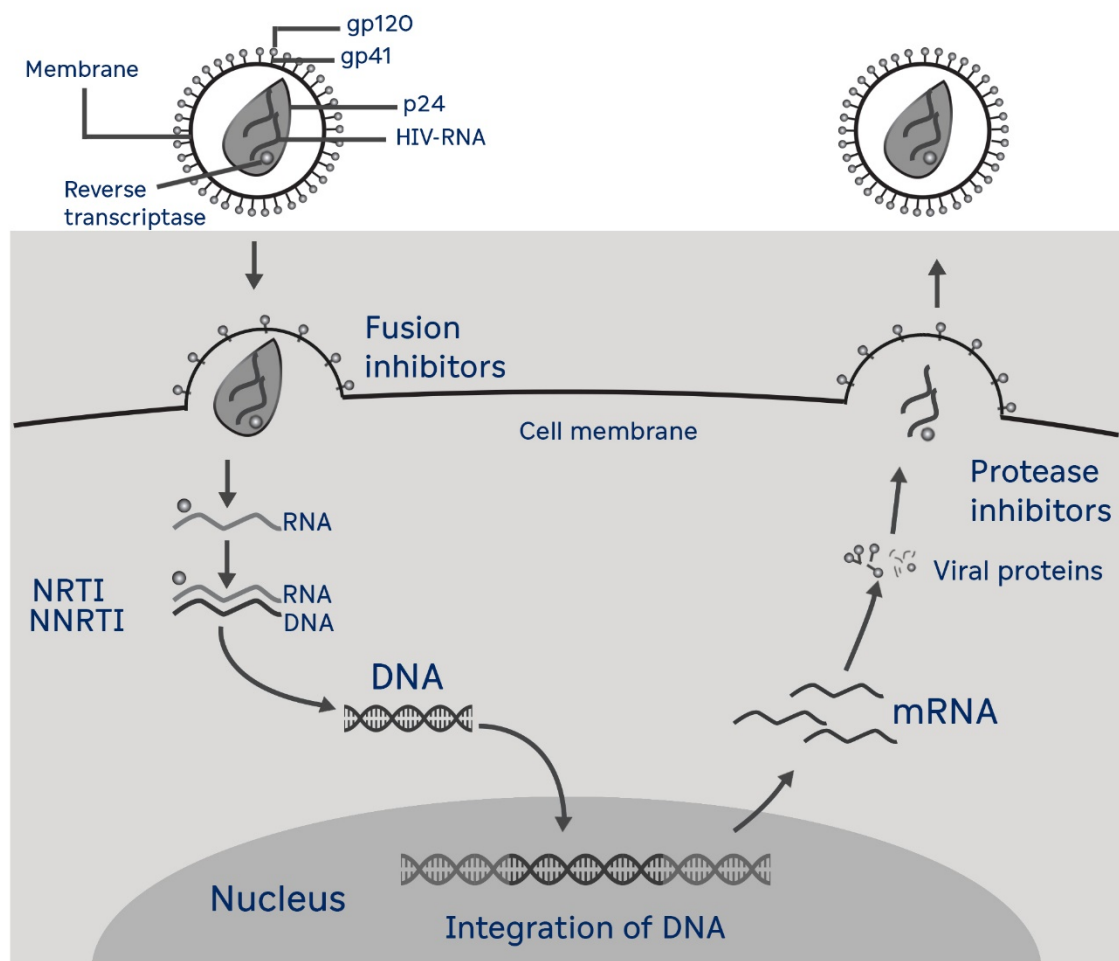


Figure 4. The lifecycle of HIV.

DNA: Deoxyribonucleic Acid; gp41: glycoprotein 41; gp120: glycoprotein 120; HIV: Human Immunodeficiency Virus; mRNA: messenger RNA; NNRTI: Non-Nucleoside Analogue Reverse Transcriptase Inhibitor; NRTI : Nucleoside Reverse Transcriptase Inhibitor; p24: p24 Antigen; RNA: Ribonucleic Acid.

Adopted from Simon et al. (154).

Clinical phases of HIV infection

Acute HIV phase

The acute phase starts within two to four weeks of the primary infection (169). During this phase, viremia sharply surges and hits a peak of 10^6 – 10^7 copies/mL blood (170, 171). However, this initial burst of viremia will decline by 100 to 1000 fold over the following two to three months until entering a steady plateau that may remain for years (170, 171). Parallel to the high viremia levels during this phase, the CD4 count decreases (172). Symptomatic cases were estimated in 40-90% of infected patients in the acute phase (173). Symptoms during this phase can include fever, fatigue, lymphadenopathy, sore throat, tonsillitis, diarrhea, and joint and muscle pain (173-177). These symptoms reflect the natural reaction to infection that can last for a few weeks (174). However, these symptoms are non-specific and can be easily mistaken with symptoms of other diseases, and hence, cannot be used to diagnose HIV. Since patients have a high level of viremia during this stage and are usually unaware of their status, they can easily transmit the disease to another person (178, 179). Regardless of the transmission mode, the virus can not be instantly detected in plasma (169). The period from acquiring the infection until the viral RNA becomes detectable in the plasma is known as "the eclipse phase" (169). This phase lasts between seven and 21 days (180, 181). Afterwards, the virus can be detected through nucleic acid amplification when the virus RNA concentration is one to five copies/mL (182) or through RNA viral loads when the viral RNA concentration is ≥ 50 copies/mL (183). The end of the acute phase is characterized by a marked drop in the viral load, to 10^3 – 10^4 copies/mL blood, along with a partial recovery for the immune system due to the increase of CD4 cells count (170, 171).

Chronic HIV phase

The chronic phase, also known as the clinical latency phase or the asymptomatic phase, is characterized by a gradual decrease in viremia and lack of symptoms. During this phase, the virus replicates at remarkably low levels. This observation is explained by the antiviral action generated by the immune system in which antibodies bind to the virus antigens to block the virus from infecting more cells (184). However, the chronic phase is also characterized by a slow and gradual reduction in the CD4 cells count, in which the loss rate exceeds the production rate. This impaired balance between the rate of CD4 cell production and loss will later contribute to the deterioration of the immune system. For patients without antiretroviral

treatment, this phase can remain for a decade or longer. However, some patients proceed throughout this phase more rapidly. Patients on antiretroviral therapy (ART) may stay in this phase for several decades with no risk of transmitting the infection. By the end of this phase, the viral load of patients increases, and the CD4 cell count decreases. As a result, the patient may establish symptoms as the virus levels rise and the patient progresses into the next phase.

Acquired immunodeficiency syndrome phase

This final phase is characterized by a marked decrease in the CD4 cell count (less than 200 cells/ μ l), a marked increase in the viral load and a weak immune system (Figure 5) (185, 186). As a result, several opportunistic infections and malignancies frequently occur during this phase due to the weakened immune system (105, 187). The most common opportunistic infections are “*Toxoplasma gondii*, *Cryptosporidium parvum*, *Pneumocystis jirovecii*, *Mycobacterium tuberculosis* and atypical mycobacteria, *Salmonella spec.*, *pneumococci*, *human polyomavirus JC*, *cytomegalovirus* (CMV) and *herpes simplex virus* (HSV)” (105). The most frequent co-infection among PLWHA is *Mycobacterium tuberculosis* (TB) (188). The risk of developing TB is 20-30 times higher among PLWHA compared to HIV-negative individuals (189). The risk of having TB increases as the level of weak immunity increases (188). The associated malignancies are Kaposi's sarcoma, non-Hodgkin's lymphomas and malignancies caused by *human papillomaviruses* (HPV) (105). Early diagnosis of opportunistic infections is necessary to control disease progression during this phase as they induce further damage to the immune system (187).

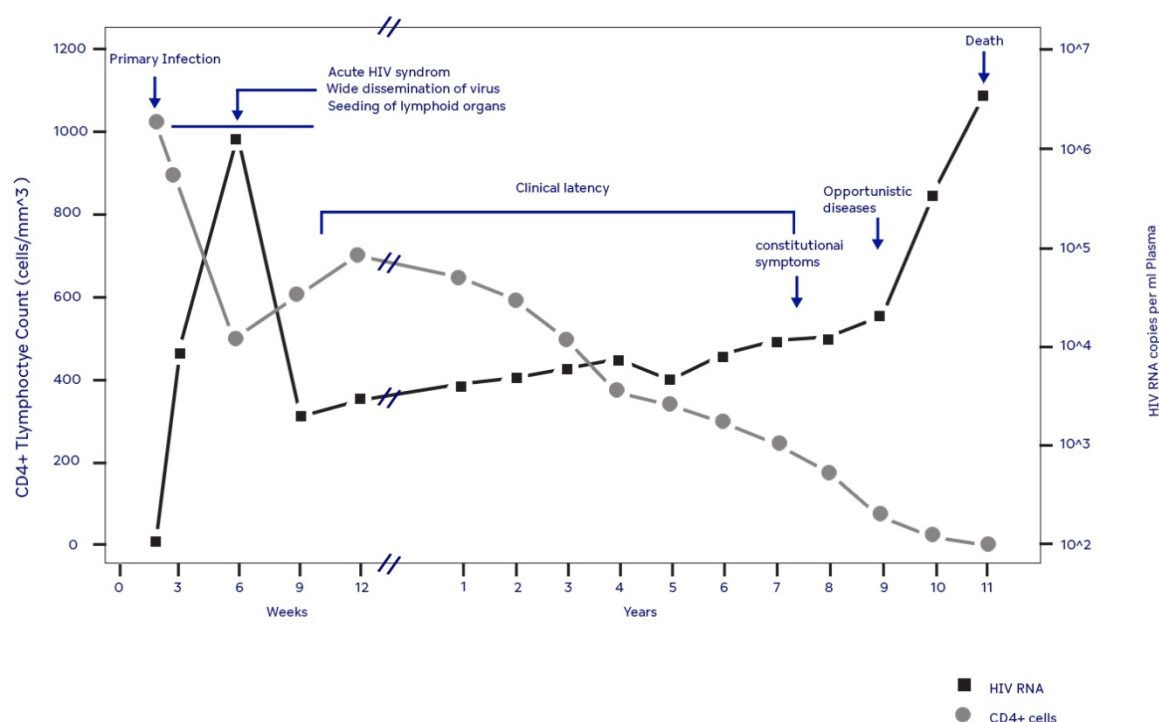


Figure 5. Progression of an untreated HIV infection.

HIV: Human Immunodeficiency Virus; RNA: Ribonucleic Acid.

Adopted from Pantaleo et al.(186).

Antiretroviral therapy

The isolation of HIV in 1983 sparked intensive research to discover medications that could suppress viral production. ART indicates the employment of antiretroviral medications to control HIV infection. Without ART, the virus impairs the immune system, and makes it vulnerable to opportunistic infections, AIDS-defining conditions and death. The introduction of ART resulted in a substantial decrease in the incidence of opportunistic infections, morbidities and mortality among PLWHA (190-192). However, previous studies indicated that controlling HIV progression is not the only clinical benefit of ART as it could mitigate the effect of non-AIDS defining illnesses, such as cardiovascular and renal conditions (193). Moreover, through controlling the viral load, ART effectively decreases levels of inflammation and coagulation biomarkers, which are associated with high levels of viremia (194). Moreover, PLWHA with undetectable viral loads due to ART adherence do not transmit HIV to their sexual partners. Given this high importance, immediate and lifetime ART is advised for all patients diagnosed with HIV, irrespective of their CD4 cells count or clinical status (195). It is

also important to mention that ART has entered a new era with the contemporary advancement of the quantification of viral replication in which viral load can be measured, allowing for the close follow-up of patients.

In 1987, a nucleoside analogue reverse transcriptase inhibitor (NRTI), known as Zidovudine (AZT), was the first ART to exhibit an effect in the clinical course of the disease (196). Nevertheless, the clinical potency was limited owing to this drug's low antiviral effect as a monotherapy. The next step was to develop a sustainable clinical effect by combining two NRTI medications. This continuous progress resulted in combination therapy between AZT and another NRTI, known as Didanosine, that led to better clinical outcomes regarding viral suppression and CD4⁺ cell counts compared to AZT therapy alone (197). Similar outcomes were achieved when combining AZT and Lamivudine, another NRTI (198). However, the first breakthrough in ART occurred in 1996 when a combination of three drugs demonstrated highly effective clinical outcomes and was introduced as highly-active antiretroviral therapy (HAART), also known as combined antiretroviral therapy (cART). This triple therapy consisted of two NRTIs and one protease inhibitor, which effectively suppressed HIV replication and enabled the immune system to recover (191). Protease inhibitors have markedly reduced viral loads, allowed immune recovery, and decreased the incidence of opportunistic infections and related mortalities (Figure 6) (192, 199).

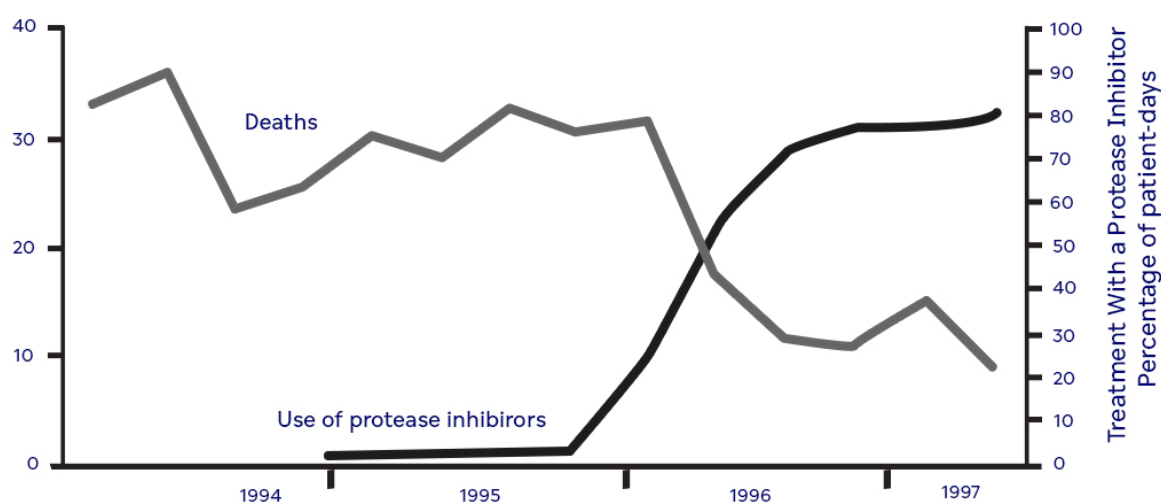


Figure 6. Decrease of HIV disease mortality after the introduction of potent combined antiretroviral therapy.

HIV: Human Immunodeficiency Virus.
Adopted from Palella Jr et al. (191).

This breakthrough was succeeded by another in which the non-nucleoside analogue reverse transcriptase inhibitor (NNRTI) replaced the protease inhibitor, resulting in significant improvements in clinical outcomes and a significant reduction in AIDS incidence and mortality (191, 200). Accordingly, and since its introduction, HAART remains the gold standard of choice for the clinical management of HIV (201-203). Table 1 shows antiretrovirals (ARV) approved by the US Food and Drug Administration (FDA), referring to nine groups and working through different mechanisms by blocking the HIV replication cycle. It is essential to mention that the use of HAART has led to a substantial decline in virus transmission, which led to the establishment of the HIV Treatment as Prevention (TasP) concept (204-207). As HAART suppresses the viral load to undetectable levels, PLWHA and on HAART as prescribed will no longer transmit the virus through sexual transmission (203, 208).

Table 1. FDA approval of HIV medicines by year.

1985-1989	1987 Zidovudine (NRTI)				
1990-1994	1991 Didanosine (NRTI)	1992 Zalcitabine (NRTI)	1994 Stavudine (NRTI)		
1995-1999	1995 Lamivudine (NRTI) Saquinavir (PI)	1996 Indinavir* (PI) Nevirapine (NNRTI) Ritonavir	1997 Combivir (FDC) Delavirdine (NNRTI) Nelfinavir (PI)	1998 Abacavir (NRTI) Efavirenz (NNRTI)	1999 Amprenavir (PI)
2000-2004	2000 Dianosine EC (NRTI) Kalerta (FDC) Trizivir (FDC)	2001 Tenofovir DF (NRTI)	2003 Atazanavir (PI) Emtricitabine (NRTI) Enfuvirtide (FI) Fosamprenavir (PI)	2004 Epzicom (FDC) Truvada (FDC)	
2005-2009	2005 Tipranavir (PI)	2006 Atripla (FDC) Darunavir (PI)	2007 Maraviroc (CA) Raltegravir (INSTA)	2008 Etravirine (NNRTI)	
2010-2014	2011 Complera (FDC)	2012 Stribild (FDC)	2013 Dolutegravir (INSTI)	2014 Cobicistat (PE) Elvitegravir (INSTI) Triumeq (FDC)	
2015-2019	2015	2016 Descovy (FDC) Odefsey (FDC)	2017 Juluca (FDC)	2018 Biktarvy (FDC) Cimduo (FDC) Delstrigo (FDC) Doravirine (NNRTI) Ibalizumab-uiyk (PAI) Symfi (FDC) Symfi LO (FDC) Symtuza (FDC) Temixys (FDC)	2019 Dovato (FDC)
2000-2001	2000 Cabenuva (FDC) Cabotegravir (INSTI)				

CA: CCR5 Antagonist; FDA: Food and Drug Administration; FDC: Fixed-Dose Combination; FI: Fusion Inhibitor; INSTI: Integrase Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI: Nucleoside Reverse Transcriptase Inhibitor; PE: Pharmacokinetic Enhancer; PI: Protease Inhibitor; PAI: Post-Attachment Inhibitor.

Data adopted from U.S. National Institutes of Health (NIH) (209).

Global timeline of HIV/AIDS

Since the first AIDS cases were reported in the US in 1981, the world has witnessed several political, economic and scientific breakthroughs aimed at mitigating the effect of the epidemic. Several advancements in HIV/AIDS antiretrovirals, policies and scientific breakthroughs have taken place in the US. However, it is important to mention these advancements timeline; given their global effect. The global timeline also includes HIV/AIDS developments and policies in Portugal.

1980s

Although the wide notion that HIV existed years before, the year 1981 is usually identified as the beginning of the epidemic. On June 5, 1981, the US Centers for Disease Control and Prevention (CDC) reported its earliest findings of *Pneumocystis carinii* pneumonia among five homosexual men in Los Angeles (210). Following the CDC's report, similar cases kept being reported to the CDC. Moreover, on July 4 of the same year, the CDC reported the occurrence of Kaposi's Sarcoma, an uncommonly reported skin malignancy, among young gay men (211). As of September 15, 1982, the CDC had recorded about 600 cases of AIDS with a subsequent 41% mortality rate (212). 1982 was also the year when the CDC established the term AIDS and released its case definition. However, the misnomer term "gay-related immune deficiency", abbreviated as GRID, was commonly used among healthcare professionals and the media, making an incorrectly essential connection between homosexuality and the disease. The same year witnessed the first AIDS case in the African continent, which later turned to be among the most affected world regions. The US held its first congressional hearing on AIDS and the first AIDS community service center on the political level.

In March 1983, guidelines for preventing transmission through blood transfusions and sexual contact were introduced in the US (213). Moreover, incentives for pharmaceutical companies to develop medications were established through the Orphan Drug Act (214). However, the same year witnessed a scientific breakthrough in which the virus causing AIDS was identified for the first time by Dr. Montagnier from France, who identified it as a lymphadenopathy-associated virus (LAV), with results published in *Science* (215). In the same year, another scientist, Dr. Gallo, isolated the virus, identified by him as HTLV-III, and proposed that a retrovirus was the infectious agent responsible for AIDS (216). Afterward, the first meeting by the WHO was held with the aim to evaluate the global impact of the disease

and to establish global surveillance measures. The first AIDS case in Portugal was also reported in the same year, 1983 (217). Given the devastating social, human and economic effects of AIDS during that time, the Denver Principles were founded with the aim of self-empowering people with AIDS who faced exclusion from their communities (218). In Portugal, the first clinical case of HIV infection was diagnosed in October 1983 (217, 219).

In June 1984, both Dr. Montagnier and Dr. Gallo held a joint press conference announcing their findings and declaring HIV as the causative agent for AIDS. In July 1984, the CDC affirmed that preventing transmission of the virus could be enhanced by avoiding sharing needles and drug injections (220). By 1985, HIV/AIDS cases were reported in all regions of the world. In the same year, Atlanta, Georgia, US, hosted the first International AIDS Conference that was organized by the WHO, the US CDC and Emory University, Atlanta, Georgia, in which around 2,000 scientists and health officials gathered to discuss the emerging new disease (221). A critical scientific breakthrough and a key milestone in the fight against HIV/AIDS occurred in 1985 through the FDA approval of the first test that could detect antibodies against HIV (222). Moreover, Public Health Service in the US published its guidelines for preventing vertical transmission (223). On the advocacy level, the same year witnessed several HIV advocacy events, such as the case of Ryan White, a teenager diagnosed with AIDS, who went on to advocate publicly against AIDS stigma and discrimination after being excluded from school following his AIDS diagnosis (224). In Portugal, and in order to evaluate the country's condition regarding HIV infection, the Ministry of Health created the AIDS Working Group in 1985, whose objectives were to collect information on new cases of HIV/AIDS infection, confirm or refute the diagnoses made, implement infection prevention strategies at a national level, and to compare the epidemic in Portugal with other European countries (225). This Working Group consisted of representatives from the Directorates-General for Primary Health Care and Hospitals, the National Blood Institute, and the National Health Institute (225).

In 1986, HIV/AIDS was declared as a national health crisis in the US that required large-scale funding plans (226). In the same year, AZT began clinical trials (227, 228). The US Surgeon General released the first report on AIDS, encouraging more health education and condom use, and offered instructions about modes of transmission and prevention in plain simple language (229). During the same year, Boston, Massachusetts, began the first informal needle exchange program (NEP) to limit the spread of the disease among the population of people who inject drugs (PWID) (230). On the international level, Paris, France, hosted the second International AIDS Conference, and the opening session was delivered by Dr.

Montagnier (231). The conference discussed the growing concerns regarding the spread of the virus in the African region for the first time by hosting prominent health experts from the African continent (231).

In 1987, the first case of HIV-2 was reported in a Portuguese hospital (Egaz Moniz, Lisbon) in a patient from Guinea-Bissau (139, 141). In the same year, FDA took several but crucial steps towards HIV/AIDS. First, the FDA approved the first ARV medication, AZT (a nucleoside analog) (196, 222, 232). Following this approval, the US authorized \$30 million to fund AZT through the country. However, the high proposed price of AZT by that time led to several demonstrations by activists groups that were mainly targeting pharmaceutical firms, which led to the creation of the AIDS Coalition to Unleash Power (ACT UP) in New York City (233). Second, the FDA established the Treatment Investigational New Drugs (INDs) clinical trial class to reduce drug approval time (222). Third, the FDA approved condoms as an HIV prevention method (222). The US government banned HIV-positive migrants from entering the country and listed HIV as a dangerous infectious disease, indicating public health concerns and the financial burden on the country's health service (231). HIV/AIDS gained global attention in the United Nations (UN) General Assembly on the international level (234). Moreover, the assembly delegated the WHO to manage the international efforts in controlling the disease (234). Washington, D.C. hosted the third International AIDS Conference, parallel to several demonstrations against the reluctant political response to HIV/AIDS (231).

In 1988, Stockholm, Sweden, hosted the fourth International AIDS Conference that witnessed the creation of the International AIDS Society (IAS) (231). The IAS aimed to promote global solidarity among HIV/AIDS experts, creating an international and interdisciplinary approach in tackling the disease, fighting discrimination against PLWHA and vulnerable populations, and supporting research for more effective prevention and treatment interventions (231). In the same year, the US National Institutes of Health (NIH) established the Office of AIDS Research (OAR) and the AIDS Clinical Trials Group (ACTG) (235, 236). The ACTG's mission was to conduct ground-breaking research to develop drugs for HIV, and its co-infections and comorbidities (236). ACTG studies, through their clinical trials units all over the world, had a significant impact on the well-being of PLWHA, as they contributed to the marked decline in HIV/AIDS mortality worldwide (236). Moreover, the FDA allowed unapproved medications for patients with critical illnesses, including HIV/AIDS (222). ACT UP protested at the FDA headquarters against the slow rate of HIV medication approval (222). The first authorized NEP was founded in Tacoma, Washington (237). On December 1, 1988, the WHO announced World AIDS Day, which was considered the first international day for

global health, as the organization reported an increase in AIDS cases by 56% worldwide (238, 239).

In 1989, the CDC released instructions for preventing *Pneumocystis carinii pneumonia*, a common AIDS-related opportunistic infection (240). In the same year, Dr. Fauci, the director of the US National Institute of Allergy and Infectious Diseases (NIAID), supported the recommendations of a parallel track policy in which patients who do not fulfill the requirements for clinical trials can have access to experimental treatments (241). Montreal, Canada, hosted the fifth International AIDS Conference under the theme “The Scientific and Social Challenge of AIDS” (231).

1990s

In the late 1980s and early 1990s, Portugal recorded one of the highest incidence rates of HIV infection in Europe (242). As of 1990, the advance of the epidemic in Portugal required the reformulation of the AIDS Working Group through the creation of a new structure, the National Commission for the Fight Against AIDS [Comissão Nacional de Luta Contra a Sida] (CNLCS) (225). The new commission was responsible for implementing new programs, policies and legislation to survey the HIV epidemic in the country, and to prevent new infections through education (225). In 1990, the US Congress established the Comprehensive AIDS Resources Emergency (CARE) Act, providing financial support for community-based care and treatment services, and assuring a comprehensive continuum of care (243). In the same year, the FDA approved AZT for pediatric AIDS cases (244). San Francisco, California, hosted the sixth International AIDS Conference, “AIDS in the Nineties: From Science to Policy”. The conference was associated with clashes between police and activists; hence the IAS recommended the importance of freedom of speech and giving more space for protesters to share their concerns (231).

In 1991, the International Council of AIDS Service Organizations (ICASO) was formed as a global hub of community-based and non-governmental HIV/AIDS organizations (245). The Red ribbon was first introduced as a symbol of AIDS awareness during the epidemic surge and as a way to support PLWHA (246, 247). Florence, Italy, hosted the seventh International AIDS Conference under the theme “Science Challenging AIDS”. This conference focused on the importance of science in curbing HIV spread, and the growing epidemic in Africa and India (231). In 1992, AIDS was announced as the first cause of death among males aged 25 to 44 years in the US (248). The same year witnessed the FDA's approval of the first rapid HIV test,

which provides results in a few minutes. In Portugal, the Regional Commission for the Fight Against AIDS was created in 1992 in Madeira's Autonomous Region (231). On the international level, Amsterdam, Netherlands, hosted the eighth International AIDS Conference, with the theme “A World United Against AIDS”. The conference focused on human rights as an important element in fighting against HIV/AIDS (231).

As of July 1993, the Portuguese Minister of Health approved the National Plan to Fight Against HIV/AIDS, which guided the action of the National Commission for the Fight Against AIDS until 2000 (225). During the same year, Portugal established its first Needle Exchange Programme (NEP) among PWID (249, 250). That year also saw several accomplishments to control HIV/AIDS among women. First, female condoms as a prevention method were approved by the FDA (251). Second, two major studies among women began in the US, HIV Epidemiology Study (HERS) (252) and Women's Interagency HIV Study (WIHS) (253). Berlin, Germany, hosted the ninth International AIDS Conference “Tear down the walls” that aimed at breaking down the barriers between PLWHA and the general population (231). Moreover, the rising concerns regarding the devastating economic effect of HIV/AIDS was one of the main topics discussed during the conference (231).

In 1994, the AIDS incidence rate in Portugal was among the highest in Western Europe (254). Moreover, Portugal decided to finance NEP through public resources (249). In 1994, AZT was recommended for pregnant women to reduce perinatal transmission as studies showed up to a 70% reduction in transmission (255). In the same year, the NIH called for the importance of including minorities and women in clinical research (256). Yokohama, Japan, hosted the 10th International AIDS Conference with the theme “The Global Challenge of AIDS: Together for the Future” (231). By that time, Japan was the only country in the Asian continent to admit having citizens living with HIV, amidst rejection and denial from the conservative society in the country.

In 1995, a breakthrough and a cornerstone in the course of HIV/AIDS treatment occurred through the FDA approval of the first protease inhibitor, Saquinavir, establishing the new phase of HAART (257). In the same year, the White House hosted its first Conference on HIV/AIDS hosted by President Bill Clinton (258). The first guidelines for the prevention of opportunistic infections among PLWHA were issued by the CDC (259). NEPs were declared an effective prevention measure against HIV after the CDC issued a report on the importance of NEPs (260).

In 1996, the Joint United Nations Programme on HIV/AIDS (UNAIDS) was established to lead and coordinate the global efforts against HIV/AIDS (261). Since its

establishment, UNAIDS has led and organized global actions and efforts against HIV/AIDS (261). In the same year, Portugal introduced HAART for the first time (262). The FDA approved a new test that could measure the body's viral load, the first HIV urine test, the first NNRTI and the first HIV home test (263). Vancouver, Canada, hosted the 11th International AIDS Conference, which emphasized HAART's effectiveness and created a new optimistic era (231).

In 1997, reported AIDS cases and AIDS-related mortalities sharply declined in developed countries in conjunction with the introduction of HAART (264). For example, the US witnessed a marked reduction in AIDS mortalities owing to the introduction of HAART, a 40% reduction when compared to 1996. Moreover, the number of reported AIDS cases in Portugal declined for the first time for the same reason, 966 cases compared to 968 cases in 2016 (265). The FDA approved a combination of two ARV in one tablet, Combivir, to improve patient compliance and adherence to medications (266). In the same year, the FDA allowed the distribution of information about off-label uses of drugs through the Modernization Act (267).

In 1998, as HAART gained substantial momentum, the first guidelines for the use of ART among adults were released by the Department of Health and Human Services. In Portugal, the AIDS Districts Commissions were created through collaboration between the Ministries of Education, Health, Labor, Solidarity and Youth (225). These structures were the response to calls for decentralizing the coordination and execution of the actions developed by the National Commission for the Fight Against AIDS (225). Moreover, the first voluntary testing and counseling center, known as “Centro de Rastreio Anónimo (CRA),” opened its doors in Lisbon, Portugal, as a pioneer center to provide free and anonymous HIV testing, along with counseling assistance for PLWHA (268). Geneva, Switzerland, hosted the 12th International AIDS Conference with the theme “Bridging the Gap”. The conference focused on treatment gaps between rich and poor, governments, and civil society (231). In 1999, the US established the LIFE initiative, which stands for Leadership and Investment in Fighting an Epidemic, to tackle the global epidemic and increase global funding (269).

2000s

During the surge of the HIV epidemic in Portugal in the late 1990s and early 2000s, new HIV infections were concentrated in PWID (242). In 2000, the AIDS incidence rate in Portugal was the highest among all of Western Europe, and this status remained until 2002 (217). Given these unfavorable conditions, the Decree-Law No. 173/2000 was issued in

Portugal to redefine the CNLCS's goals, restructure the commission's body, and reallocate the existing resources (225). Moreover, a new coordinator was appointed to achieve these changes, according to Decree-Law No. 57/2000 (225). These new goals included improving research activities to cover areas with knowledge gaps and developing the process of dissemination of information regarding the epidemic in Portugal. In the same year, following the success of CRA Lisbon, CRA Faro was established in the South of the country, in continuation of the concept adopted in Lisbon (268). Durban, South Africa, hosted the 13th International AIDS Conference, themed "Breaking the Silence" to raise awareness of the global pandemic. The conference focused on the disproportionate burden of HIV/AIDS in sub-Saharan Africa, and inequity in distribution and access to HAART between developed and developing countries (231). The year 2000 witnessed several initiatives involving collaboration between several international entities to overcome the growing global pandemic. For example, HIV/AIDS was acknowledged as a security threat by the UN Security Council (270). The Global AIDS Relief Act was approved by the US, providing about \$600 million as a global fund for the efforts against AIDS/HIV (271). The Group of Eight (G8) summit, which refers to the group of eight highly industrialized nations, declared the necessity for further financial resources (272). The WHO, UNAIDS and global entities established a collaboration with several pharmaceutical corporations to decrease ARV prices in developing countries. Moreover, the US announced an executive order to help developing countries in making generic HIV medications (273). The CDC established the Global AIDS Program (GAP) to build effective alliances with multiple effective global partners (274). The global efforts against HIV/AIDS have culminated in 2000 when the UN declared the eight Millennium Development Goals (MDGs), with MDG six focusing on fight HIV/AIDS, malaria, and other diseases (275).

In 2001, Portugal's AIDS incidence rate remained the highest in Western Europe, with almost 106 cases per million inhabitants (217, 276). Accordingly, the country adopted progressive drug policies to curb infection among PWID, one of the country's most affected populations. These policies included the decriminalization of personal drug use with an aim to shift the focus on drug use from criminal justice to public health (242). Moreover, the Portuguese CNLCS framed the "Strategic Plan for the Fight against HIV/AIDS" to guide its actions through the 2001-2003 triennium. In accordance with this strategic plan, the CRA centers that had been implemented throughout the national territory were renamed as Counseling and Early Detection Centers for HIV infection, known as "Centros de Aconselhamento e Detecção Precoce da Infecção VIH" (CAD). These aimed to provide free, and anonymous HIV testing, along with counseling assistance (268). On the international level,

the UN Secretary-General stressed the importance of a global fund to tackle HIV/AIDS, during the African Summit on HIV/AIDS in Abuja, Nigeria (277).

In 2002, Portugal became the President of the UN's Coordinating Council Program against AIDS (UNAIDS). In the same year, women accounted for almost half of PLWHA, and HIV/AIDS was the main cause of death among individuals between 15 and 59 years worldwide. The first wave of the global fund to fight against AIDS, TB and malaria started during the same year (278). Barcelona, Spain, hosted the 14th International AIDS Conference themed "Knowledge and Commitment", which witnessed a marked contribution by women and participants from developing countries (231).

On July 1, 2003, CNLCS was restructured into a Mission Unit through the Council of Minister's Legislation No. 121/2003, to better coordinate and monitor the fight against HIV/AIDS in Portugal (225). The US President's Emergency Plan for AIDS Relief, known as PEPFAR, was created, which is one of the most effective initiatives and dedication by any country to tackle a particular disease in history. This accelerated progression toward controlling the global HIV/AIDS epidemic (279). The initiative has saved over 20 million lives and prevented millions of new infections through about \$85 billion investments directed at curbing the global epidemic in more than 50 countries (280). The G8 Summit was held in Évian-les-Bains, France, and a further contribution to the Global Fund was declared in the same year (281). A new plan, known as the 3 by 5 Initiative, was announced by the WHO to extend HIV treatment to an additional three million individuals (282).

In 2004, and given the devastating global effect of HIV/AIDS, the UN Secretary-General put the fight against AIDS on the same level of importance as the fight against terror, and considered the global epidemic a threat to international peace and security (283). Additionally, the UN called for exploring the expected effects of HIV/AIDS on countries and communities, and defining required long-term actions towards controlling the epidemic through scientific research (283). During the same year, UNAIDS initiated the Global Coalition on Women and AIDS to draw attention to the devastating effect of HIV/AIDS among females and girls, and stimulate effective and practical action to control the spread of HIV among women. By that time, nearly half of the adult PLWHA were women (284). Bangkok, Thailand, hosted the 15th International AIDS Conference. The conference themed "Access for All" drew attention to the importance of universal access to HIV prevention, care and treatment interventions (231). Bangkok also hosted the first Partnership Forum for the Global Fund to Fight AIDS, Tuberculosis and Malaria during the same year (285). The Forum is a special feature of the Global Fund that represents its governance structure.

In 2005, the Portuguese CNLCS was dissolved and integrated into the High Commissioner for Health through Decree-law No. 7/2005 (286). This action aimed for better vertical coordination of the involved institutions and more effective horizontal articulation with other players and sectors whose efforts are crucial for achieving better results (225). The duties of the CNLCS are carried out by the National Coordinator for HIV/AIDS program on August 25, 2005, led by Dr. Barros (225). This new entity aimed to afford technical assistance to policymakers and create the National Health Plan (287). Furthermore, a new declaration in 2005 made it mandatory to integrate HIV infection into the list of mandatory reported diseases (288). The new declaration considered that the short- and medium-term monitoring and projection of HIV infection is fundamental for its prevention and control, which is only feasible with the knowledge of the epidemiological pattern of HIV infection in Portugal (288). Accordingly, the Ministry of Health made it mandatory to report any stage of the HIV infection, AIDS-related complex (ARC), AIDS diagnosis or AIDS-related deaths (288). The economic effect of HIV/AIDS in Africa and other heavily affected regions was among the subjects discussed at the World Economic Forum in Davos, Switzerland. Several global entities and organizations, including the WHO, UNAIDS and the Global Fund, published results of international cooperation and joint efforts to expand the coverage of ARVs in developing countries, with around 700,000 individuals to be covered by the end of 2004 (289).

In 2006, five years after the 2001 UN's special session, the UN published a report on progress in the global HIV/AIDS response, specified critical challenges and made important recommendations to coordinate global efforts (290). The report showed a significant variation among countries in achieving key targets of the 2001 declaration. However, the report listed several achievements made against HIV/AIDS, such as broader access to treatment and prevention measures (290). Toronto, Canada, hosted the 16th International AIDS Conference, themed "Time to Deliver". The conference shed light on the weak global response against the epidemic despite the available resources and almost 25 years of experience. Moreover, the conference called for improving prevention efforts through addressing gender inequality, stigma and discrimination against high-risk populations (231).

In 2007, the WHO and UNAIDS stressed the importance of expanding HIV testing and recommended male circumcision as a preventive measure (291). The international clinical trial, iPrEx, started at several sites to study if a daily dose of ARVs can decrease the risk of acquiring HIV among men who have sex with men (MSM) and transgender women who have sex with men (292). In 2008, Mexico City, Mexico hosted the 17th International AIDS Conference, themed "Universal Action Now", the first conference to be hosted by a Latin American country

(231). In 2009, the US established the Global Health Initiative to address global health in developing countries with HIV/AIDS as a main target (293).

2010s

In 2010, the iPrEx clinical trial revealed that a daily combination of two ARVs (emtricitabine/tenofovir disoproxil fumarate) could effectively and safely reduce the risk of acquiring HIV among MSM and transgender women who have sex with men (292). Another randomized clinical trial, CAPRISA 004, showed that the risk of HIV infection among women could be reduced by using a topical gel with 1% tenofovir (294). Vienna, Austria, hosted the 18th International AIDS Conference in the same year, themed “Rights Here, Right Now”, and focused on the importance of human rights as a crucial aspect in the fight against HIV/AIDS. The same year witnessed calls for new international drug policies in accordance with science and not ideology, and these calls culminated with the signing of the Vienna Declaration (231).

In 2011, a phase III, randomized clinical trial, known as HPTN 052, showed that the nearly treatment of heterosexual PWLHA with ART could reduce HIV transmission among their serodiscordant couples (295). In the same year, Portugal established CheckpointLX in Lisbon, a community-based center for anonymous and free rapid HIV testing and counselling, targeted at MSM, one of the country's most affected groups (296). This center was recognized by the WHO and the European Center for Disease Prevention and Control (ECDC) as a new and innovative service in Portugal that reflects the need of addressing the epidemic among vulnerable populations, which is in line with the national action plan to combat HIV/AIDS (297, 298). The center was considered a cost-effective strategy for increasing the detection of new HIV cases in MSM (299).

In 2012, Washington, D.C., hosted the 19th International AIDS Conference (231). In the same year, the FDA approved a breakthrough on the prevention level by authorizing the combination of two ARVs, emtricitabine and tenofovir disoproxil fumarate, known as Truvada, to prevent HIV infection in HIV negative individuals, a concept known as pre-exposure prophylaxis (PrEP) (300). Moreover, the FDA approved the first rapid test using oral fluid (301).

In 2013, UNAIDS announced that AIDS mortalities had been reduced by about 30% since 2005 (302). In the same year, a study found that the early start of ART improves the health outcomes of PLWHA (303). Additionally, the WHO updated the previous standard timing for starting ARVs, from CD4 cell count of 350 cells/mm³ to 500 cells/mm³ (304).

In 2014, UNAIDS declared the 90-90-90 targets in which 90% of all PLWHA will be diagnosed, 90% of all PLWHA who are diagnosed will receive ART, and 90% of those treated will achieve viral suppression by 2020 (305). In 2014, the US Public Health Services released guidelines and recommendations for offering PrEP as a prevention option for several key populations, including MSM, demonstrating the importance of such a strategy in curbing HIV among MSM (306, 307). Melbourne, Australia, hosted the 20th International AIDS Conference in 2014, under the theme of “Stepping up the Pace” (308).

In 2015, the UN declared the new Sustainable Development Goals (SDGs) (309), with a specific target to eliminate the AIDS epidemic by 2030 (310). Two additional clinical trials, namely Ipergay and PROUD, showed PrEP as an effective way to prevent HIV transmission among MSM (311, 312). The WHO updated the standard timing for starting ARVs to start immediately when the diagnosis is made, regardless of the CD4 count, a concept known as treat all (313). Accordingly, Portugal implemented the treat all concept by providing free ART to any individual diagnosed with HIV regardless of the infection stage (242).

In 2016, PrEP was approved by the European Medicines Agency and became available in several countries, including Portugal (314). The UN Member States declared a new political statement towards ending the epidemic (315). This political statement introduced a list of specific targets with defined time frames to end the AIDS epidemic by 2030. Durban, South Africa, hosted the 21st International AIDS Conference under the theme “Access Equity Rights Now” reflecting the importance of providing comprehensive HIV services to everyone in need (316). The Global Fund approved around \$13 billion as additional support for the fight against HIV/AIDS (317). Sweden became the first UN Member State to reach 90-90-90 targets (318). HIV incidences in Portugal dropped from almost 2000 cases in 2007 to nearly 1000 in 2016, recording a 50% reduction in a decade (242).

In 2017, the UN announced new pricing arrangements as a guarantee to afford the first generic, single-pill ARV scheme in low- and middle-income countries (319). Portugal adopted PrEP as a new prevention measure in the fight against HIV, especially among high-risk populations in 2017 (242). Moreover, Portugal achieved UNAIDS 90-90-90 targets in 2017 as 92.2% of PLWHA were diagnosed, of those diagnosed, 90.3% were on ART, and of those treated, 93.0% achieved viral suppression (320).

Since February 2018, PrEP became available and fully reimbursed through the National Health Service (NHS) in Portugal (314). Amsterdam, Netherlands, hosted the 22nd International AIDS Conference, themed “Breaking Barriers, Building Bridges”. The theme aimed to highlight the need for measures that guarantee effective communication with high-

risk populations (321). The 23rd International AIDS Conference (AIDS 2020) was the first AIDS Conference to be held on a virtual base due to the unprecedented COVID-19 pandemic (322).

The global HIV epidemic

Since the world became aware of AIDS in 1981, the infection has spread; therefore, at the end of 2019, the disease had claimed 33 million lives with around 38 million PLHWA across the globe (323). The global prevalence of HIV/AIDS among adults was estimated to be 0.7% in 2019 (324). Over 67% of all PLWHA live in the WHO African Region, almost 25.7 million. Figure 7 shows that sub-Saharan Africa carries the heaviest burden of HIV, followed by Asia and the Pacific (324).



Figure 7. Adult HIV prevalence, 2019.
Reproduced from the Kaiser Family Foundation (324).

Table 2 shows the HIV prevalence, incidence and the number of AIDS-related deaths by region (324).

Table 2. HIV global prevalence in 2019.

Region	Adult prevalence	Number of people living with HIV (% of global total)	Number of people newly infected with HIV	Number of AIDS-related deaths
Global, Total	0.7%	38.0 million (100%)	1.7 million	690,000
Eastern and Southern Africa	6.7%	20.7 million (54%)	730,000	300,000
Western and Central Africa	1.4%	4.9 million (13%)	240,000	140,000
Asia and the Pacific	0.2%	5.8 million (15%)	300,000	160,000
Western and Central Europe and North America	0.2%	2.2 million (6%)	65,000	12,000
Latin America	0.4%	2.1 million (6%)	120,000	37,000
Eastern Europe and Central Asia	0.9%	1.7 million (4%)	170,000	35,000
The Caribbean	1.1%	330,000 (<1%)	13,000	6,900
Middle East and North Africa	<0.1%	240,000 (<1%)	20,000	8,000

AIDS: Acquired Immunodeficiency Syndrome; HIV: Human Immunodeficiency Virus.

Data Source Kaiser Family Foundation (324).

HIV incidence has decreased by 39% between 1999, which witnessed the peak of HIV incidence, and 2019, with 3,160,000 and 1,700,000 cases, respectively (325, 326). Moreover, the number of annual deaths from HIV/AIDS has significantly decreased from 1,950,000 during its peak in 2006 to 690,000 in 2019 (325, 326). Regarding treatment coverage, and owing to the international attempts to respond to HIV/AIDS, the global coverage of lifelong ART has been rising steadily. About 70% of adult PLHWA and more than 50% of children living with HIV are on ART treatment worldwide (323). Moreover, about 85% of pregnant and breastfeeding women living with HIV were on ART in 2019, improving their health and preventing mother-to-child viral transmission through viral load suppression (323). The number of PLHWA who are on ART has increased from 2,980,000 in 2006 to 25,400,00 in 2019 (325, 326). These accomplishments resulted from comprehensive efforts by international organizations, governments, patient groups and community partners, as elaborated in the global timeline of HIV/AIDS. These efforts have resulted in a substantial increase in the number of PLHWA from 8,740,000 in 1990 to 38,000,000 in 2019 (325, 326). Regarding achieving the UN 90-90-90 targets, about 81% of PLHWA were diagnosed by the end of 2019, 67% of those diagnosed were receiving ART, and 59% of those on ART achieved viral suppression (323). Regarding the epidemic in the European Region, 137,000 new cases were recorded in Member States in 2019, with almost 25,000 new infections in the EU/European Economic Area (EEA), corresponding to around 15 new diagnosed cases per 100,000 population (Figure 8) (327).

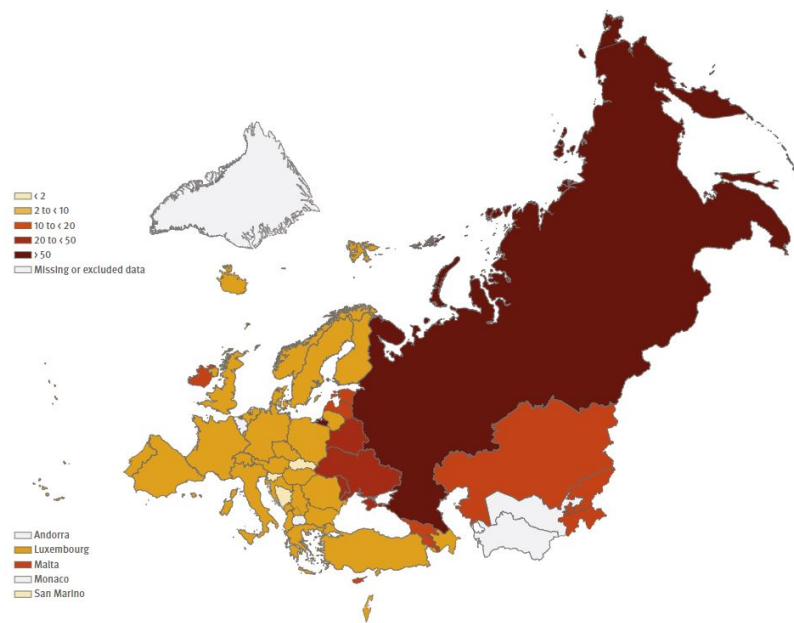


Figure 8. Distribution of HIV diagnoses per 100,000 population in Europe, 2019.

HIV: Human Immunodeficiency Virus.

Source: European Centre for Disease Prevention and Control (ECDC) (327).

HIV is concentrated in specific populations who are at high risk of acquiring the infection in all countries. These populations include MSM, transgender people, PWID, sex workers, migrants and people in prisons. In 2019, over 60% of new global HIV infections were reported in these key populations and their sexual partners, and may reach 95% in specific regions (323). Other key populations in specific regions include girls and young women in some African countries (323). The mode of HIV transmission varies by region. For example, the main route of transmission in sub-Saharan Africa is through heterosexual transmission (323). The mode of transmission in Western Europe tends to be more diverse when compared to sub-Saharan Africa with a considerable proportion of transmission attributed to MSM, migrants (Figure 9), and PWID (328). Since the beginning of the HIV epidemic, MSM were one of the main populations affected by the disease (329, 330). Migrants in the EU/EEA accounted for 44% of new HIV diagnoses in 2019 (327). A considerable proportion of migrants acquire the infection after arriving in the EU/EEA (331-333), which highlights the need for prevention measures for migrant populations (334).

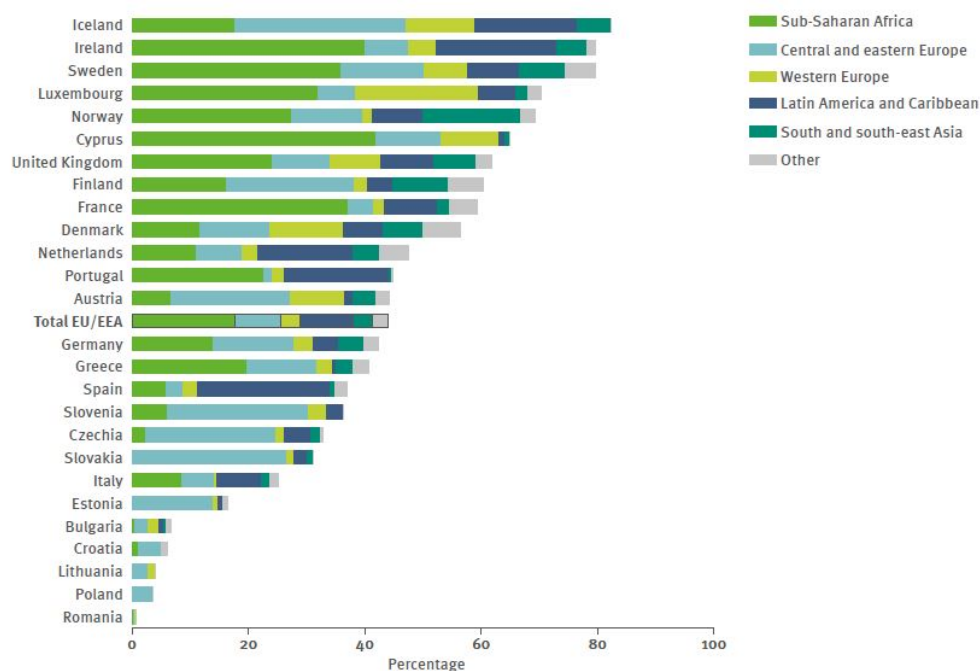


Figure 9. Percentage of new HIV diagnoses among migrants in the EU/EEA by region, 2019.

EU/EEA: European Union/European Economic Area; HIV: Human Immunodeficiency Virus.

Source: World Health Organization (327).

The HIV epidemic in Portugal

Portugal made remarkable achievements in the health sector in the last decades, resulting from political and economic investments in healthcare (335). Despite these achievements, HIV continues to be a major public health concern as the country is recording one of the most severe epidemics in Western Europe (Figure 10) (262, 336). Between 1983 and 2020, 61,433 cases of HIV infection were diagnosed in Portugal, of which 22,835 reported cases of AIDS and 15,213 reported deaths (336). By the end of 2018, 41,305 PLWHA were estimated in Portugal (336). The proportion of undiagnosed infections was higher among heterosexual men (13.1%) and lower among PWID (1.4%) (336). The average time between infection and diagnosis was 3.4 years (320). By the end of 2018, the adjusted national prevalence of HIV was 0.40% [95% confidence interval (CI): 0.40-0.41%] (336). In addition, it was estimated that 2,807 (95% CI: 2,475-3,206) infections would not yet have been diagnosed, which is equivalent to 6.8% (95% CI: 6.0-7.7%) of PLWHA by the end of 2018 (336). Temporal trends in Portugal showed a steady decrease in both new HIV and AIDS diagnoses between 2009 and 2018, 47% and 65%, respectively (336). Despite these downward

trends, Portugal is still exhibiting one of the highest rates of new HIV and AIDS diagnosis among EU countries (327). The HIV-1 virus corresponds to 95.4% of the total accumulated cases (58,596 cases) until 2019, with HIV-2 accounting for 3.3% (2,030 cases) (336). Most of the diagnosed cases in 2019 occurred in individuals who were born in Portugal (55.7%).

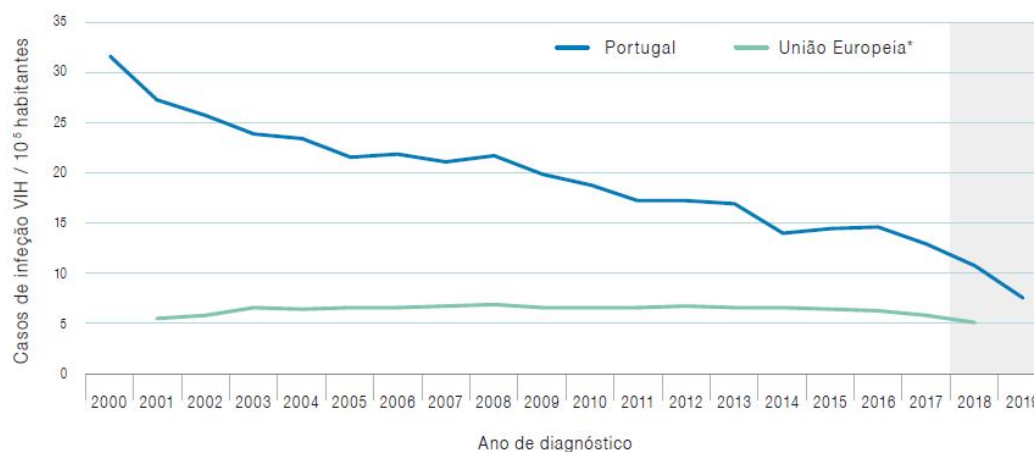


Figure 10. HIV infection incidence in Portugal and the European Union by year (2000-2018).

HIV: Human Immunodeficiency Virus.

Source: Ministry of Health, Portugal (320).

In 2019, 778 new cases of HIV infection were reported in Portugal, which corresponds to a rate of 7.6 cases per 100,000 inhabitants, not adjusted for the delay in notification (336). The new diagnoses were 2.3 times higher in males than in females (336). The median age at the time of diagnosis was 38 years, and about 24% of new cases occurred among individuals 50 years or older (336). The highest diagnostic rate was found among the 25-29 age group, 22.1 cases per 100,000 population. Around half of new cases were located in the Metropolitan Area of Lisbon, which corresponds to 13.7 cases per 100,000 population, followed by the Algarve region with 13.5 cases per 100,000. Similar to previous years, the majority of new cases occurred through heterosexual transmission. Although most of the newly diagnosed cases in 2018 were asymptomatic at the first clinical evaluation, an associated AIDS diagnosis occurred in 15% of new cases. The prevalence of resistance mutations to any drug class was 14.6% among newly diagnosed cases, with mutations to NNRTI being the most frequent (11.2%) (320). During 2019, 172 new AIDS cases (1.7 per 100,000 people) were diagnosed among individuals aged 15 years or above, in which *Pneumocystis jirovecii* pneumonia was the most frequent AIDS-defining illness (320). Moreover, 197 deaths occurred in individuals

with HIV infection in 2019. Deaths occurring in the five years following the diagnosis accounted for 22.8% of the total number of deaths (320).

As in the rest of the world, the HIV epidemic in Portugal is highly concentrated in certain populations who are at high risk of acquiring the infection, such as MSM, migrants and PWID (337). Previous studies estimated the prevalence of HIV among MSM in Portugal to be around 11% (338, 339). Since 2015, cases among MSM correspond to the majority of cases reported in men, exceeding the new cases among heterosexual men (Figure 11). For example, the MSM population, which represents only 3% of the adult male population, accounted for 56.7% of new diagnoses in all men in 2019. New cases among MSM had the lowest median age (30 years) and corresponded to 65.2% of the cases diagnosed in individuals under 30 years of age (336). The number of new HIV diagnoses in young MSM draw attention to and reinforce the need for focused strategies for this specific population (336). The substantial burden of HIV among MSM in Portugal suggests that current existing strategies for HIV prevention are not sufficient, hence, demonstrating the urgent need for more effective prevention strategies. Transmission among PWID showed a steady increase since the beginning of the epidemic until its peak in 1999, with almost 1800 cases reported among this group in the same year. Afterwards, newly diagnosed cases among this group declined sharply to only 16 cases in 2019 (Figure 11).

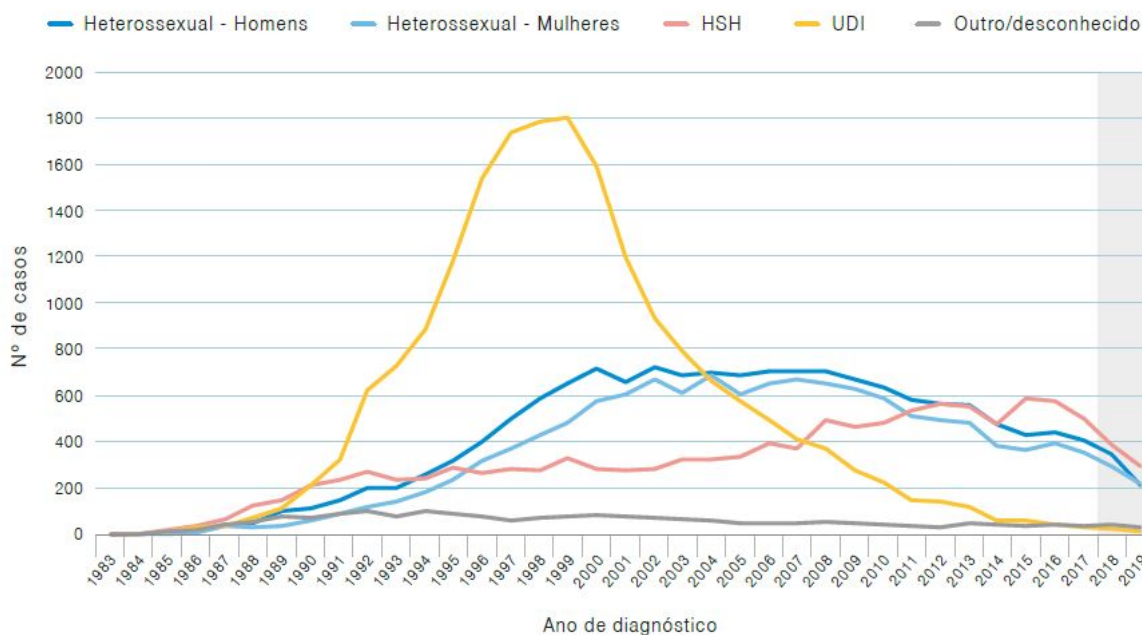


Figure 11. HIV infection cases in Portugal according to mode of transmission and year of diagnosis (1983 to 2018).

HIV: Human Immunodeficiency Virus.

Source: Ministry of Health, Portugal (320).

Migrants in Portugal represent another aspect of the concentrated epidemic, as they are more likely to be exposed to the infection and less likely to access prevention measures (340, 341). The HIV epidemic among migrants in Portugal is more likely to be linked to heterosexual transmission, especially among migrants from countries with high HIV prevalence (341). Migrants in Portugal account for about 20% of the country's total prevalence, contributing to a disproportionate proportion of heterosexually transmission (340). Moreover, migrants in Portugal accounted for about 45% of newly diagnosed infections reported in 2019 (327).

Figure 12 shows the most frequent AIDS-defining illnesses according to the mode of transmission. *Pneumocystis pneumonia* is the most associated AIDS-defining illness among heterosexuals (35.5%) and MSM (44.4%), while pulmonary and extra-pulmonary tuberculosis were the most common among PWID (30.8% for each).

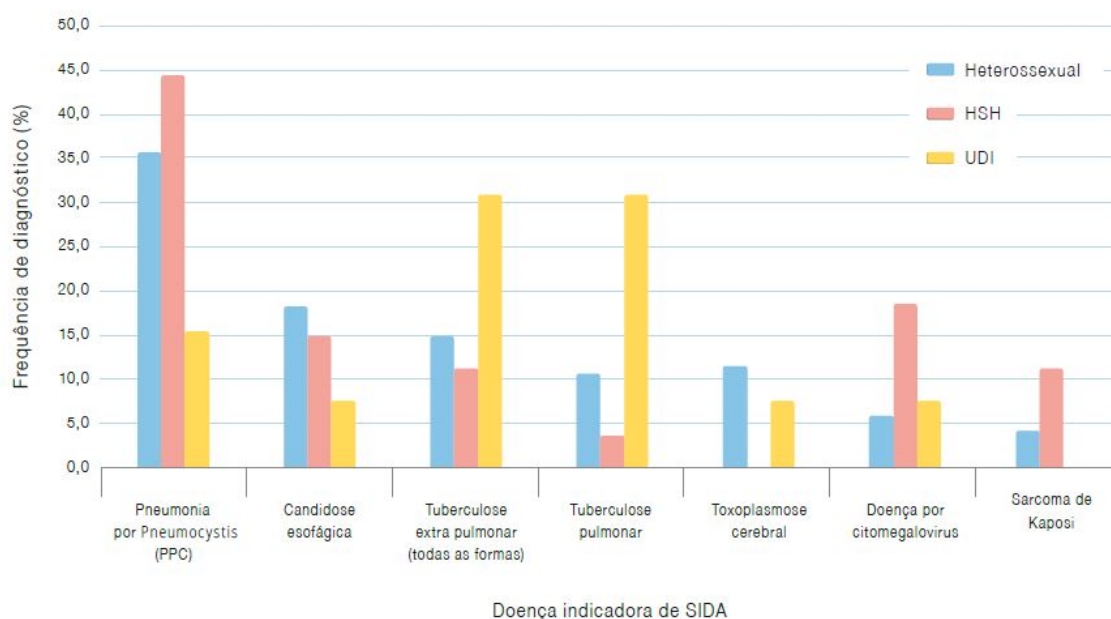


Figure 12. Most common AIDS-defining diseases (1983-2018): frequency of diagnosis of the most common diseases according to the mode of transmission of HIV infection.

AIDS: Acquired Immunodeficiency Syndrome; HIV: Human Immunodeficiency Virus.

Source: Ministry of Health, Portugal (320).

Portugal achieved the HIV targets set by the UNAIDS, known as the 90-90-90 targets in 2017 (320). Data showed that 92.2% of PLWHA in Portugal were diagnosed in 2017; of those who were diagnosed 90.3% were treated, and of those who were treated 93.0% achieved viral suppression (320). However, despite these achievements, the national response to

HIV/AIDS needs to continue adopting measures and interventions to end the epidemic in the country. For example, in 2018, around five million male condoms, 750 thousand female condoms and one million three hundred thousand syringes were distributed, and about 1,000 individuals, mostly males, started HIV PrEP (320). About 50 thousand rapid HIV tests were carried out in different health facilities and community-based locations, with an increase of about 28% compared to 2017 (320).

The economic impact and burden of HIV/AIDS

Since the world became aware of AIDS in the early 80s, the disease has caused overwhelming damage to populations' health, families and governments, and has been listed as the most significant single economic burden on healthcare systems globally (342-344). HIV created substantial pressure on health systems as it consumes a considerable amount of resources (345). However, the disease did not only devastate populations' health, but it also created socioeconomic problems all over the world (343, 344). As HIV infection is more visible in individuals of working age, it leads to the deterioration of productivity and human capital due to morbidities and premature deaths among working forces (346, 347). In many countries, the disease represents a heavy burden for households who struggle to afford treatment costs due to long-term illness or comorbidities. The available evidence indicates that HIV/AIDS represents a heavy economic burden on households as treatment costs consume households' savings and resources (348-350). This income loss due to treatment costs may affect households' investments in food, agriculture or education (351, 352).

The relation between HIV/AIDS and economics used to be bi-directional in which HIV/AIDS affects the economy at both the macro and micro levels, and simultaneously, economic conditions can significantly affect HIV/AIDS (353). An example of how the economy affects HIV/AIDS is the economic crisis of 2011 that led to austerity measures in several countries, resulting in cuts in health budgets that later downsized HIV/AIDS national programs (17). An example of how the economy can be affected by HIV/AIDS are the morbidities and deaths among labour forces due to HIV/AIDS-related causes that lead to productivity loss (346, 347, 350, 351).

The introduction of HAART was associated with increased concerns about the costs of care for PLWHA (354-361). This historic breakthrough fundamentally changed the life expectancy and quality of life of PLWHA (345, 362). However, HAART has created serious

challenges for health systems and public health worldwide (363). From an economic standpoint, HAART has imposed a financial burden in an era of universal access to treatment and a sharp reduction in HIV/AIDS mortality. In other words, this growth in treatment cost was due to the conversion of HIV/AIDS from a fatal to a chronic illness; thus, it requires sustainable long-term care for PLWHA (201, 351, 362, 364, 365). It is also important to mention that if HAART is a cost-effective intervention, as shown in previous economic evaluation studies (364, 366), this does not mean that the cost of this intervention does not concern governments as it still requires the allocation of sufficient resources (345). Moreover, previous studies have shown that HAART can cause a wide array of side effects, such as nephro-hepatic, gastrointestinal and metabolic side effects that require treatment, and thus, imply additional costs (345, 367, 368). Furthermore, the dynamic introduction of new and expensive ARVs implies an additional burden on governments as they need to allocate further resources to meet updated therapy standards (345). All these factors have increased the cost of treating PLWHA over time (99, 369). Finally, the disproportionate number of newly diagnosed members of key populations adds a burden on the health system every year as they require lifelong treatment (363). Given this burden, HIV/AIDS has become a priority for health systems across the world. Thus governments have set different strategies to prevent HIV infections, given the anticipated economic returns (353). Accordingly, it was of paramount importance to provide precise and updated information regarding HIV/AIDS care costs to guide health policymakers' decisions with planning and resource allocation (370). Moreover, given the importance of HIV/AIDS as a threat to global health, articulating global efforts through the UNAIDS MDGs and SDGs was necessary (371-373).

Between 2000 and 2015, the global direct spending on HIV/AIDS reached about \$560 billion, whereas the degree of expenditures differs considerably by country, income and disease prevalence (371). However, the actual economic burden may considerably surpass this value as it does not include indirect costs and household costs (374, 375). The direct healthcare costs, also known as provider costs, include costs of ART; hospitalizations, laboratory exams; and medical consultations. The indirect costs of HIV/AIDS can include productivity loss, such as loss of labour time due to morbidity related to HIV and time spent by informal caregivers or household members caring for PLWHA (350, 375). The household's spending includes medical and non-medical expenses, such as transportation and special dietary needs (350, 375).

Most HIV/AIDS spending takes place in high- and upper-middle-income countries, although most PLWHA are in lower-middle- and low-income countries (371). In 2015, high- and upper-middle-income countries spent \$31.3 billion on HIV/AIDS, while lower-middle-

and low-income countries spent \$17.8 billion (371). Governments carry a substantial burden when it comes to spending on HIV/AIDS as they are responsible for developing fundamental prevention and treatment programs. Governments worldwide contributed to 61% of the total spending on HIV/AIDS, followed by development assistance for health (29.7%), out-of-pocket (6.5%) and private sources (2.8%) (Figure 13) (376).

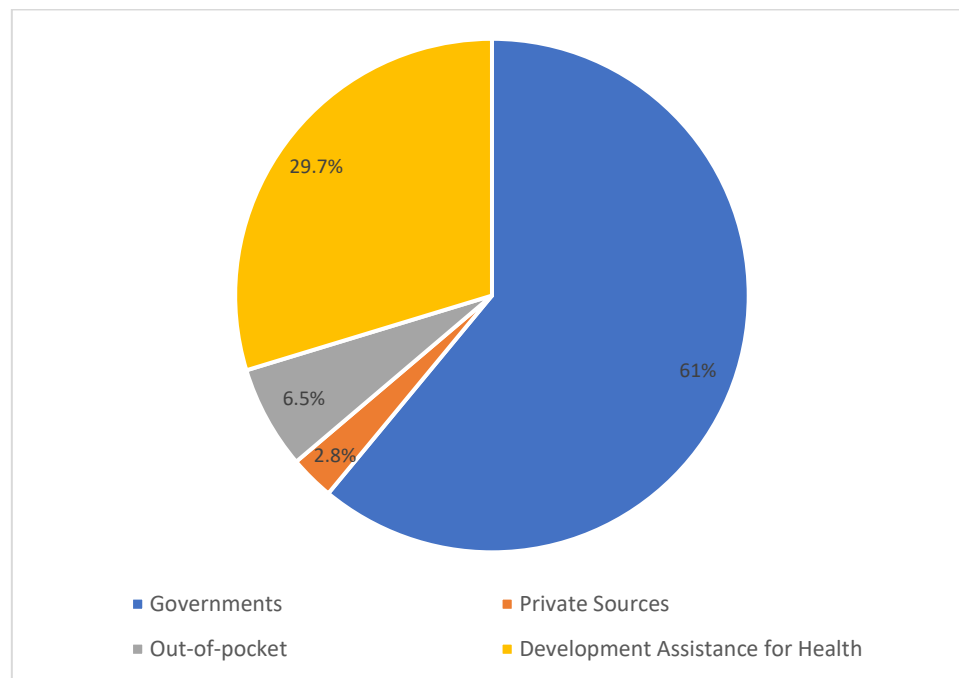


Figure 13. Global spending on HIV/AIDS by source, 2015.

AIDS: Acquired Immunodeficiency Syndrome; HIV: Human Immunodeficiency Virus.

Source of data: Financing Global Health Database (376).

Although high-income countries are home to only 9.4% of PLWHA, they account for almost 34% of the total global spending on HIV/AIDS. On the contrary, low-income countries, home to nearly 30% of PLWHA, account for only 16.4% of the total global spending on HIV/AIDS (371). HIV/AIDS care and treatment services include outpatient care, inpatient care, and the cost of ART. (371). The total spending on HIV/AIDS care and treatment services has steadily increased from \$8.1 billion in 2000 to around \$27 billion in 2015 (Figure 14) (376). In 2015, spending on care and treatment services accounted for over 50% of all spending on HIV/AIDS (Figure 14) (376). Moreover, spending on prevention measures, such as general public health programs and programs to prevent transmission among most at high-risk populations has grown significantly. Spending on prevention programs amounted to \$4.0

billion in 2000, which increased to \$9.3 billion in 2015, or 19.0% of all HIV/AIDS spending (371).

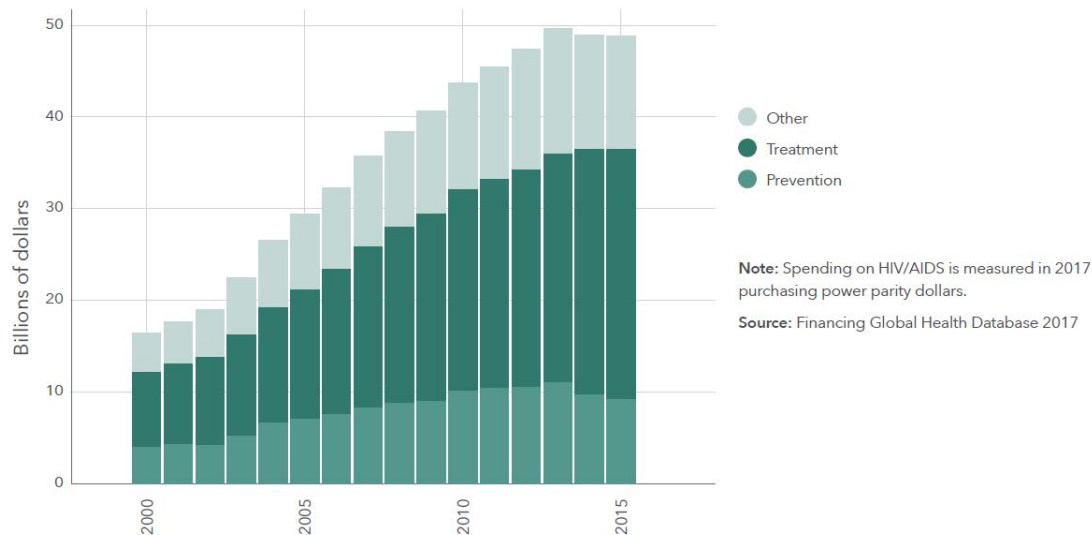


Figure 14. Spending on HIV/AIDS by type, 2000–2015.

AIDS: Acquired Immunodeficiency Syndrome; HIV: Human Immunodeficiency Virus.

Source: Financing Global Health Database (376).

Diagnosis-related groups

DRGs are a patient classification system for inpatient hospital care in which patients are grouped according to several criteria, such as principal diagnosis, secondary diagnosis/es, applied procedures, patient's age, sex, co-morbidities, complications, discharge status and expected inpatient LOS (377). DRGs regulate payments to hospitals and promote cost containment initiatives. It is assumed that patients grouped within the same DRG will have similar hospital resource utilization, thus requiring an equal reimbursement scheme with a fixed value irrespective of the actual values acquired to improve quality of care (378, 379). The payment of DRGs covers all costs associated with inpatient stays from the time of admission to discharge (380). This system reflects a process of measuring hospital production as a means of evaluating what takes place in the hospital (381). The objective of DRGs is to classify patients into relatively homogeneous groups from the point of view of clinical characteristics and associated consumption of resources, in order to enable the identification of outliers. This perspective of improving hospital quality was first initiated by Dr. Codman, a pioneering Massachusetts physician and best known as the father of hospital outcomes management, at

the beginning of the 20th century (380, 382). Dr. Codman was acknowledged for his contribution in tracking hospital outcomes and patient complications through measuring morbidity and mortality outcomes (383). Consequently, quality and hospital performance measures have been widely implemented among hospitals as payers began demanding healthcare based on quality, thus reducing health expenditure. However, the development and implementation of the modern version of DRGs has been widely credited to Dr. Fetter, an industrial engineer from Yale University, when he started to develop a scheme of healthcare utilization and quality of care for the Yale University Hospital in 1965 (384). However, it was only in 1983 when the Medicare program decided to implement DRGs on a large scale, after long preparations that required developments in hospital information technology to process big sets of hospital data (385). By October 1983, Medicare established the Prospective Payment System (PPS), in which hospitals are paid a fixed amount per discharge according to a patient's DRG and included 1500 hospitals in the first phase (386). By September 1984, Medicare added 3700 hospitals to the PPS (386). Including DRGs in Medicare as a new prospective payment system is praised as "the single most influential post-war innovation in medical financing", for its role in balancing the power between healthcare providers and third-party payers as it guarantees efficiency in healthcare spending (387).

Currently, there are several major versions of the DRGs in use that include basic DRGs, Refined DRGs (R-DRGs), All Patient DRGs (AP-DRGs), All Patient Refined DRGs (APR-DRGs), Severity DRGs (S-DRGs), All-Patient Refined DRGs (APR-DRG) and International Refined DRGs (IR-DRG) (378, 381, 388).

Table 3. Different DRG systems.

DRG System Version	Description
Basic DRGs	Used by Medicare and measure the typical resource use of an inpatient stay for patients over 56 years of age.
Refined DRGs (R-DRG)	Including a revision of the use of complications and co-morbidities.
All-Patient DRGs (AP-DRG)	Extension of DRGs from Medicare population to include all patients. AP-DRGs are similar to DRGs, but also include a more detailed DRG breakdown for non-Medicare patients, particularly newborns and children.
Severity DRGs (S-DRG)	Re-evaluation of the use of complications and co-morbidities for Medicare DRGs according to severity.
All-Patient Refined DRGs (APR-DRG)	Further refinement of all-patient DRGs adding subgroups and re-evaluating the use of complications and co-morbidities. The APR-DRG structure is similar to the AP-DRG, but also measures severity of illness and risk of mortality in addition to resource utilization.
International Refined DRGs (IR-DRG)	New classification system allowing international comparisons regardless of the specific coding system of the country.

DRG: Diagnosis-Related Group.

Adopted from Böcking et al., Kobel et al., and Shafrin et al. (378, 381, 388).

A patient's classification within DRGs requires computerized software applications and a standardized coding system, such as the International Classification of Diseases (ICD), to classify diagnoses and procedures performed. Coding diseases and procedures according to the ICD supports decision-making and the reimbursement process by allowing better collection and analysis of data (389). The ICD version varies between countries and according to the DRG in use (390). DRGs may be further grouped into Major Diagnostic Categories (MDCs). MDCs are formed by dividing all possible principal diagnoses from ICD into 23 to 25 mutually exclusive diagnosis groups (381).

Diagnostic-related groups in Europe

Similar to the US, the move towards a DRGs-based hospital payment system in other countries aimed at incentivizing hospitals to improve quality of care and enhance their performance (391, 392). The global influence of the progress toward the DRGs scheme was rapid, especially in Europe. Since 1983, DRG-based payment schemes have been adopted as the basis for reimbursing hospitals and measuring their performance in Europe, despite modifications applied to the original version created in the US by creating algorithms and grouping of episodes for this purpose (380, 393). In 1984, a meeting was held in France to discuss the application of DRGs in Europe, which included Dr. Fetter, and involved France, Netherlands, Belgium, Ireland and Portugal (380). This meeting was followed by another meeting in Dublin, Ireland, in 1986 that included 11 European countries, and a third meeting in Lisbon, Portugal, in 1987 that had included 15 European countries. These meetings and discussions concerning the importance of DRGs inspired the creation of the Patient Classification Systems International (PCSI) and the Patient Classifications Systems Europe (PCSE) in 1987 in Lisbon (394). This growing attention towards DRGs has also motivated scholars, academics and insurers worldwide to study and develop the concept of grouping similar patients within the health system (394).

Given this importance, several international and European organizations have developed initiatives to advance and apply DRGs systems. For example, in 1985, the Council of Europe established a review of the research being undertaken in Europe on DRGs, which aimed to evaluate the possibility of applying this concept on a larger scale. In addition, the Organization for Economic Co-operation and Development (OECD) established publishing international reports on LOS according to DRGs with the objective of comparing performance according to LOS (395). Furthermore, the EU established a program during the late 1980s

concerned with assisting health research and supporting several projects linked to cost, DRGs and supporting the development of patient classification systems suitable for European hospitals (385, 396). During the same period, the WHO supported several meetings regarding the use of DRGs for hospital budgeting and performance measurement (397). Portugal was the first country to fully apply a DRGs-based hospital payment scheme in Europe, including almost 30% of public hospitals in 1988. Norway was the second to apply the DRGs payment system in 1991 (398), and Ireland started a limited DRGs budget allocation system in 1993 (380).

Diagnostic related groups in Portugal

DRGs were first introduced in Portuguese hospitals through a pilot study in 1984 (399, 400). The project was a result of cooperation between the Portuguese Ministry of Health and the US Agency for International Development (UNAID) (386). To assess the possibility of adapting the American model to the Portuguese system, the Health Systems Management Group, under the direction of Dr. Fetter, and the American company Solon Consulting Group Ltd, acquired later by 3M™, under the direction of Dr. Vertrees were consulted (386). 3M™ is an American multinational company operating in several fields that include US healthcare (401). The was introduced Portugal through the Ministry of Health, and overseen by Dr. Urbano and colleagues (402). The Ministry of Health aimed to improve the quality of care, promote the efficient use of resources in public hospitals, and to decrease health expenditure through connecting utilized resources for inpatient care to hospital outcomes (399, 403). Implementing DRGs in Portugal aimed to increase transparency and vindicate the allocation of resources to NHS hospitals by connecting inpatient care resources to hospital outcomes (399). With a fixed payment for each DRG, hospitals face a clear incentive to minimize the resources devoted to each admission (399, 403). The application of DRGs in Portugal required developing an information technology system that enabled measuring and controlling the productivity and resource utilization of hospitals. The project then managed the communication of the information collected within hospitals, between hospitals and central administrations, and among central administrations (399).

In 1989, the first large-scale application of DRGs among Portuguese hospitals was carried out to reimburse hospitalization. In the same year, the Ministry of Health announced Legislation No. 1/89, in which the classification of patients according to DRGs became mandatory. Monthly information on the DRGs of all NHS hospitals is collected in order to integrate the National DRGs Database through the Portuguese Central Health System

Administration (ACSS). The first DRGs price tables were approved by Ordinance No. 409/90 and were applied to NHS hospitals. Since August 2006, there is only one non-modified version of DRGs in use in Portugal, known as All Patients DRGs version 21 (AP-DRGs version 21). The AP-DRGs version 21 was introduced through Law No. 567/2006. This version is part of the family of DRGs that were originally used in New York State in 1988 (400). This is implemented in all Portuguese NHS hospitals, and applies to all inpatients and ambulatory surgeries with an exception for patients treated in psychiatric and rehabilitation care settings (399). It was developed following the extension of the state's prospective payment for DRGs to all patients in acute hospitals (and not only to Medicare beneficiaries, patients aged 65 or over). AP-DRGs version 21 introduced significant changes in obstetrics, newborns, transplants, burns, and most importantly, HIV patients. For this reason, it was concluded that it would be better suited to the spectrum of patients admitted to Portuguese NHS hospitals (386). The AP-DRGs version 21 includes 669 DRGs under 25 MDCs, and each MDC refers to one organ or physiological system, with MDC 24 corresponding to HIV infection (399). Since 1984, diagnoses and procedures within the DRG system have been coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and since 2016 they have been coded using its 10th revision (ICD-10-CM) (399, 404).

Aims

Quantifying the rates and risks of hospital quality performance measures among HIV hospitalizations is of particular importance given the high demand for healthcare services and limited health resources. As such, assessing these quality measures has important implications for defining policy priorities and controlling unnecessary health expenditures. However, understanding how HIV hospitalization contributes to public health spending requires reviewing the economic burden of these hospitalizations and how they could affect the health system. Further, estimating these measures requires the use of advanced methodology, which considers the statistical nature and distribution of these quality indicators, and the variation in the quality provided by different hospitals.

In Portugal, where some of the highest prevalence and incidence rates of HIV in Europe are found, hospitalizations among HIV patients are classified as the second major diagnostic category. Moreover, in the last four decades, the country witnessed fundamental changes in the course of HIV/AIDS among patients, due to the introduction of ART. Strategies that allow access to more high-quality information regarding hospital quality indicators may contribute to improve our understanding of how to control these hospitalizations.

Therefore, this thesis we aimed to provide evidence to answer the following research questions:

1. What are the factors related to quality performance measures among HIV/AIDS hospitalizations in Portugal?
2. Do quality outcomes among HIV/AIDS hospitalizations vary by hospitals and over time in Portugal?

These will be accomplished through the following specific objectives:

- 1) To review the economic burden of HIV in Portugal, and to explain the role quality measures can play to control hospitalizations among HIV patients in Portugal (*Paper I*);

- 2) To explain the additional economic burden caused by the COVID-19 pandemic on the Portuguese health system (*Paper II*);
- 3) To quantify the association between 30-day readmission and socioeconomic/demographic, clinical and other factors (*Paper III*);
- 4) To compare the quality and performance of hospitals in Portugal based on 30-day readmission rate (*Paper III*);
- 5) To compare statistical models for analyzing LOS among HIV hospitalizations in Portugal to choose the best fitting model (*Paper IV*);
- 6) To quantify the association between prolonged LOS and socioeconomic/demographic, clinical and other factors (*Paper IV*);
- 7) To compare the quality of hospitals in Portugal based on LOS among HIV hospitalizations (*Paper IV*).

Research Methods

Data sources

The objectives of this thesis were accomplished through the analysis of data obtained from the Portuguese ACSS (405). The selection of participants to be used in each analysis depended on the specific objectives of the investigations and is described in detail in the methods sections of each manuscript. A general description of the participants and methods are provided below.

The data were collected as part of the national registry of discharges among the Portuguese NHS facilities. The data are anonymous; refer to AP-DRGs version 21, a non-modified version of AP-DRG in use in Portugal since 2006 and introduced through Regulation No. 567/2006 (406).

The collection and validation of the DRG database in Portugal are carried out through several internal and external auditing steps to ensure high-quality data, a criterion necessary for any DRG system (399). Coding in Portugal is first standardized and performed by physicians with specific training in coding (399). An internal auditor assigned by each hospital supervises data collection and the coding process. Afterward, the external coding auditing process begins with trained physicians supervised by a senior manager from the ACSS to assist and monitor the internal auditing process (399). Moreover, this external auditing team is authorized to carry out visits to hospitals and validate patient records to ensure the DRG coding and classification have been done correctly (399). It is also important to mention that the DRG clinical coding process is carried out through computer software that allows identifying data errors and discrepancies in hospital records (399). Afterwards, this software delivers data regarding the mean number of codes per record, the proportion of incorrect codes and coding errors, as well as notifying the operator of deficient information within the records, such as duplicates, undefined primary diagnosis or atypical LOS (399). A unique fictional code included in the data for data validation that allows determining how many episodes correspond to the same user in the same institution is also used, and hence avoids duplicates. This fictional code does not identify the user or allow its identification afterward.

Variables

Paper III

Dependent variable

To determine 30-day readmission for each hospitalization, a unique fictional code was used to allow determining how many episodes correspond to the same user, in the same institution. This fictional code does not identify the user nor allow its identification afterward. Accordingly, readmission episodes and the time span between readmission and the last discharge can be calculated for each hospitalization. Thus, the dependent variable of interest was created as follows: $Y = 0$ if hospitalizations without subsequent 30-day readmission, $Y = 1$ if hospitalizations with subsequent 30-day readmission(s).

Independent variables

Each record in the data corresponds to a discharge episode and contains information collected while patients were admitted to the hospital, such as information collected during hospitalization that includes sociodemographic characteristics (age, sex, region of residence), dates of hospitalization and discharge, index hospitalization, admission type (urgent or scheduled), type of intervention (surgical or medical), type of diagnosis (primary and secondary diagnoses), type of procedures during the hospitalization, prior healthcare utilization (mode of transfer, destination after discharge), outcome at discharge (alive or deceased), and coverage by the NHS.

Paper IV

Dependent variable

The dependent variable is LOS, which is defined as the number of days between in-patient admission and hospital discharge.

Independent variables

To assess the effect of covariates on LOS, information on patients, clinical characteristics and admission characteristics were extracted from the hospital discharge database. The following potential determinants of LOS were considered: age (1 = “18–29”, 2

= “30–39”, 3 = “40–49”, 4 = “50–59”, 5 = “60–69”, 6 = “≥70”), gender (0 = male, 1 = female), region (0 = Non-resident, 1 = Norte, 2 = Centro, 3 = Lisbon, 4 = Alentejo, 5 = Algarve), HIV/AIDS as a primary diagnosis (0 = no, 1 = yes), having national health coverage (SNS) (0 = no, 1 = yes), admission status (0 = elective, 1 = emergency), treatment classification (0 = medical, 1 = surgical), number of diagnoses (0 = “≤5”, 1 = “6–8”, 2 = “9–12”, 3 = “>12”), number of procedures (0 = “≤4”, 1 = “5–7”, 2 = “8–9”, 3 = “>9”), in-hospital death (0 = no, 1 = yes), transferred admission (0 = no, 1 = yes), 30-day readmission (0 = no, 1 = yes), TB (0 = no, 1 = yes), hepatitis B (0 = no, 1 = yes), hepatitis C (0 = no, 1 = yes), pneumocystis (0 = no, 1 = yes), cytomegalovirus (0 = no, 1 = yes), mycobacterial disease (0 = no, 1 = yes), toxoplasmosis (0 = no, 1 = yes), candidiasis (0 = no, 1 = yes), Kaposi’s sarcoma (0 = no, 1 = yes), history of recurrent pneumonia (0 = no, 1 = yes), weight loss (0 = no, 1 = yes), asymptomatic HIV (0 = no, 1 = yes). Since several hospitals were merged into one hospital during the period between 2009 and 2017, a dummy variable (Merge) was created to categorize hospitals according to the merging status (0 = not merged, 1 = merged) to be able to study the effect of merging on hospital quality. A dummy variable was created for the years of admission in which years before the financial crisis and bailout in Portugal were coded as 0 (2009, 2010 and 2011), while years after the financial bailout were coded as 1 (2012, 2013, 2014, 2015, 2016 and 2017).

Statistical models

For objective 1, we assessed the economic burden of hospitalizations among PLWHA in Portugal by reviewing the cost of treating HIV/AIDS, including hospitalizations, prevalence and incidence of the disease in the country (*Paper I*). In the same paper, we reviewed the possible quality measures that can control hospitalizations among PLWHA in Portugal, namely 30-day readmission and LOS. *Paper I* also pointed to the crucial need to study the factors that can further push this financial burden by assessing the factors that can affect hospital quality indicators as a first step to control spending. A general procedure for statistical analyses was purposed for the project, depending on the specific objectives of the subprojects.

For objective 2, we assessed the possible effects of the COVID-19 pandemic on the Portuguese health system (*Paper II*). An assessment of the Portuguese health system’s infrastructure, human resources, capacities and outflows was made. We also explained the possible effect of the inevitable global recession on the health system due to COVID-19, in

light of present predictions and past experience with similar economic crises. Additionally, we provided measures that can help mitigate the financial consequences of the COVID-19 pandemic on the Portuguese health system by reviewing the importance of hospital quality measures as a method for cost containment.

For objectives 3 and 4, we included a total of 37,134 registered discharges in Portuguese NHS facilities, between January 1, 2009 and December 31, 2014, with HIV/AIDS as a main or secondary cause of admission. HIV-related admissions were identified using ICD-9-CM diagnosis codes (042, V08). Univariate and multivariate logistic models were used to identify the determinants of hospitalizations with subsequent 30-day readmission by computing odds ratio (OR) and the corresponding 95% CIs. A random-effects model (also known as a multi-level model or hierarchical model) was used to determine unmeasured factors specific to each hospital, and hence, to determine the variation in 30-day readmission propensity between hospitals. A detailed statistical description of the random-effects model is included in *Paper III*. Hospital case-mix index (CMI) from B to F was combined with all hospitals in our study. The CMI reflects the clinical complexity of a particular inpatient population in a medical care environment, and it measures the relative costs and resources needed to treat the inpatient population (407). In our study, hospitals with CMI B are considered to receive patients in less complicated conditions while hospitals with CMI E are considered to receive patients in worst conditions. Group F refers to hospitals treating specific diseases, such as oncological institutes. We included a prediction model by measuring the area under the Receiver Operating Characteristics curve (AUC–ROC). AUC–ROC curve is a performance measurement for a classification problem at various threshold settings. ROC is a probability curve and AUC represents the degree or measure of separability. The curve indicates the ability of the model to distinguish between classes. In logistic regression, the higher the AUC, the better the model is at discriminating between discharges with and without 30-day readmissions. All analyses were conducted with STATA[®], version 11.2 (StataCorp LP, College Station, Texas, USA), and RStudio[®] (library MASS).

For objectives 5-7, registered discharges in Portuguese NHS facilities, between January 1, 2009 and December 31, 2017, with a total of 26,505 admissions, with HIV/AIDS as a main or secondary cause of admission were used to predict LOS among HIV hospitalizations in Portugal. We considered only discharges classified under the MDC created for patients with HIV infection (MDC 24). The dependent variable in our study was LOS, which is defined as the number of days between in-patient admission and hospital discharge. Several strategies were applied to select the best count fit model, including the *Poisson* regression model, the

zero-inflated *Poisson*, the negative binomial regression model and the zero-inflated negative binomial regression model. Model performance and estimates of precision for each of the models were calculated. After choosing the most appropriate count technique, and in addition to the fixed patient and clinical related factors, we incorporated a random hospital effects term to the negative binomial model to examine dependence between observations within the same hospital. Multiple comparisons of hospital effects were done by constructing 95% CI for random-effects. All analyses were conducted with STATA[®], version 13 (StataCorp LP, College Station, Texas, USA), and MLwiN[®], version 3.04 (University of Bristol, Bristol, UK). MLwiN is a specialized software package for fitting multilevel models.

Ethics

Data collection and all statistical methods were performed in accordance with the relevant guidelines and regulations on anonymized data sets. This is a secondary analysis of data routinely collected in Portuguese public hospitals, which was conducted under the supervision of the ACSS, the legal owner of the DRG database in Portugal. The Ethics Committee of the Institute of Hygiene and Tropical Medicine (IHMT), Lisbon, waived the requirement for written informed consent for participants in this study due to the anonymous and confidential nature of the data obtained from the ACSS in which the authors cannot identify any subject in that database, in accordance with the national legislation, the institutional requirements and the Portuguese National Authority of Data Protection for the creation of an individual database.

Paper I



The Importance of Improving the Quality of Care Among HIV/AIDS Hospitalizations in Portugal

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HIV affects almost 37.9 million persons globally, and an estimated 1.7 million new HIV infections occur in 2018 (1). While HIV/AIDS is taking a devastating toll on populations' health, lives and families, the disease is imposing a serious economic burden on governments (2–4) being classified as the greatest single financial burden on healthcare systems globally (5). This burden is predominantly due to the high payments of antiretroviral therapy (ART), hospitalizations, and associated opportunistic infections treatment (6, 7). In Portugal, HIV continues to be a major public health concern and HIV prevalence is among the highest in Europe (8, 9) with 41,000 individuals who are living with HIV, representing 0.5% of the total population (10) (see Table 1 for an informative overview of HIV/AIDS in Portugal). The country also still records annual rates of new HIV/AIDS diagnosis, which have been classified among the highest in the European Union (EU) (8). Admissions among HIV/AIDS patients still pose considerable challenges to the Portuguese national health system (5, 11). In Portugal, hospitalizations related to HIV/AIDS are some of the most expensive with an average daily cost of €825 and an average length of stay of 23 days, placing HIV/AIDS as the second greatest Major Diagnostic Category (MDC) (5, 12). In addition, and after the financial crisis that hit Portugal in 2011, the country went through strict fiscal austerity that resulted in budget cuts, reduction of spending on sensitive health sectors, and restructuring numerous public entities including the National AIDS Program (NAP) (12–14). It is important to know that the average cost of HIV treatment in Portugal is about 14,000 €/patient per year (6). The main cost driver is the antiretroviral medications (€9,598), followed by hospitalizations (€1,323). Treatment costs grow with the severity of disease from €11,901, with a CD4 count more than 500, to €23,351, with a CD4 count <50 (6). In other words, while cost related to antiretroviral remains constant over the course of the disease, the cost progression remains mainly linked to the associated hospitalizations and admissions related to HIV. Moreover, the shift of HIV infection from a fatal disease into a chronic illness carries substantial challenges to the health system. The introduction of antiretroviral therapy (ART) has dramatically increased the life expectancy of HIV patients (15–17). This modification in the natural evolution of HIV infection has led to a substantial increase in the financial burden and cost due to the net increase in the number of people living with HIV and the associated life-long treatment and comorbidities (16, 18).

TABLE 1 | HIV/AIDS estimates in Portugal.

Adults aged 15 and over living with HIV	41,000 (CI: 36,000–46,000)
Adult aged 15–49 HIV prevalence rate	0.5 (CI: 0.4–0.5)
HIV incidence per 1,000 population (adults 15–49)	0.10
People living with HIV who are on ART	37,000
Percent of people living with HIV who are on ART	90 (CI: 78–95)
Average cost of HIV treatment per year	14,277 €/patient*

Sources: UNAIDS, *Peralman et al. (6).

CI, Confidence Interval.

In this context, one possible solution to overcome this associated economic burden is to increase value in healthcare by integrating quality measures of hospitals' performance while reducing the costs of healthcare. Previous reviews supported the evidence that there is great potential for decreasing costs by targeting deficiencies in quality, and accordingly we can maximize the benefits given the available resources (19–24). Two important quality measures had obtained growing attention as a benchmark indicator for measuring hospital's performance, thirty-day readmission rate, and length of stay (LOS) (22, 25–28). However, despite being optimal methods for assessing hospital's performance, there remains a scarcity of research pertaining to the factors that can influence these quality indicators, especially when it comes to assessing hospitalizations among HIV/AIDS patients in Portugal. Thirty-day hospital readmission is defined as an episode in which a patient is readmitted within 30 days from the last discharge. Early readmission rates have increasingly been used as an outcome measure in health services research and as a quality benchmark for health systems (29–31). However, although often preventable, early readmissions have been recognized as frequent and costly events (32–34). For example, in the United States, one in five Medicare beneficiaries has 30-days readmission, with a cost of around \$26 billion per year (34, 35). Accordingly, hospital readmission rates were incorporated in the reimbursement decisions for several programs, in which the health systems penalize hospitals with higher than expected readmission rates (33, 36).

The second quality indicator is length of stay which is defined as the number of days a patient is hospitalized in relation to the admission diagnosis and it had been widely used to evaluate the effect of implementing patient group related reimbursement systems in the form of Diagnosis Related Groups systems (DRG) is length of stay (37, 38). This quality indicator has been recommended as an important outcome measure for quality improvement activities (28). Using length of stay as a hospital performance measure will allow us to impact cost and quality through payment incentives for hospitals or health care providers. For example, if a hospital reduces length of stay and accordingly the other associated resources and costs, the hospitals will be more efficient through maintaining a higher marginal return on each per admission payment (22).

The Portuguese national database of admissions among HIV patients can be obtained for research purposes from the Administration of the Health System (ACSS) (39). These

data are anonymous, refers to the Diagnosis Related Groups (DRGs), and each record corresponds to a discharge episode and contains information collected while the patients were admitted to the hospital. These data include information about length of stay as well as information collected during the hospitalization that include socio-demographic characteristics (age, sex, region of residence), dates of hospitalization and discharge, Index hospitalization (admission type (urgent or scheduled), type of intervention (surgical or medical), type of diagnosis (primary and secondary diagnoses), type of procedures during the hospitalization), prior health care utilization (mode of transfer, destination after discharge), outcome at discharge (alive or deceased), coverage by the national health system (Yes/No). To determine 30-day readmission for each hospitalization, a unique fictional code included in the data can be used since it allows determining how many episodes correspond to the same user, in the same institution. This fictional code does not identify the user nor allow its identification afterward. Accordingly, readmission episodes and the time span between the readmission and the last discharge can be calculated for each hospitalization. accordingly, The variable of interest can be created as follows: $Y = 0$ if hospitalizations without subsequent 30-day readmission, $Y = 1$ if hospitalizations with subsequent 30-day readmission(s). Univariate and multivariate logistic models can be estimated afterward to identify the determinants of hospitalizations with subsequent 30-day readmission.

Regarding length of stay, each hospitalization is associated with a record that refers to the number of days each person remains at hospital as a count data. However, giving the statistical nature of length of stay as count data, caution should be taken when handling such data with count distribution [for an informative overview of count distribution see (40)]. Using the most common techniques, namely the ordinary least squares (OLS) or logistic regression to handle a dependent variable with positive skewness as occurs in LOS, will violate the fundamental assumptions behind each technique (41, 42). Accordingly, this may result in biased and inefficient estimates and produce results that do not accurately reflect the observed data (41, 42). Fortunately, count statistical techniques (Poisson, negative binomial, Zero Inflated Poisson, and Zero Inflated Negative Binomial models) have been developed to handle count data on a dependent variable and can replace these suboptimal statistical strategies (43, 44). Using these count regression techniques will allow us to accurately determine the factors that can push length of stay further. Moreover, the conceptual and statistical advantages of each count model should be illustrated precisely since the accuracy and nature of results tend to vary depending on the specific model utilized.

This opinion contributes to the attempts on reducing the economic burden of HIV in Portugal, which is in line with Portugal's policy of cost reduction as a target to stabilize the economic situation. Our opinion point to other concerns that need to be considered: integration of quality measures as a method of evaluating hospitals' performance is crucial in the light of limited resources and should be considered as a national priority. A considerable work should be devoted to controlling and investigating the factors which tend to push 30-day

admission rate and length of stay expenses further. The statistical nature of quality measures requires a deep understanding of the appropriate statistical models that should be used to avoid biased estimates. Finally, there is a potential in policy decision-making concerning the optimal use of limited resources and as a first step, we should deeply investigate the determinants of 30-days readmission and length of stay among HIV patients in Portugal.

AUTHOR CONTRIBUTIONS

AS conceived the work, reviewed literature, and wrote the manuscript. MM supervised the work and wrote the

manuscript. All the authors have agreed on the final version of the manuscript.

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Paper II



COVID-19: What Is Next for Portugal?

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Highly infectious with the possibility of causing severe respiratory complications, the novel COVID-19 began stretching health systems beyond their capacity all over the world and pushing them to breaking points. Giving the devastating effects caused by this infection, unprecedented measures have to be adopted in order to mitigate its impacts on the health system. This perspective aims to review the epidemic of COVID-19 in Portugal, possible areas of improvement, and potential interventions that can help to mitigate the effect of COVID-19 on the Portuguese health system.

Keywords: COVID-19, health inequalities, health system, quality indicators—healthcare, mental health, economic crisis

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By June 3, 2020, the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) has infected 33,261 individuals with 1,447 mortalities in Portugal (1). Unfortunately, this crisis came shortly after the recent recovery from the financial crisis that heavily affected the country in 2011, during which Portugal was obligated to sign-up for a bailout program from several funding entities, including the European Central Bank and the International Monetary Fund (2, 3). Accordingly, the country went through strict fiscal austerity that resulted in proposing unprecedented implementations of social expense cuts and continuous cuts to public expenditure on health care (2, 4, 5). Given the expectations of inevitable global recession due to COVID-19, which may surpass the global recession of 2009 to 2011 (6–8), it is expected that once again the health system in Portugal may become a target for cost containment in the long run. In general, and during economic crises, the health sector became vulnerable and a target for budget cuts owing to its size and the high potential for improved performance (3). Estimates regarding the economic impact of the COVID-19 in Portugal, if the crisis remains until mid-June, forecast GDP decline in 2020 of –6.9% (95% confidence interval: –9.2 to –4.6%) (7). These estimates predict Portugal to be among the most affected by the crisis in comparison to other countries such as Brazil, China, or the United States, owing to the high contribution of tourism to the Portuguese economy (7). We can understand from these estimates that, even if the current containment measures, namely, quarantines and social distancing, succeed in controlling the outbreak in Portugal, the economic implications of this crisis will affect the country in a post COVID-19 era. Some early results of the economic slowdown due to COVID-19 included a decline in the real estate market in regions with the greatest dynamism in the housing market and tourism, namely, the Lisbon Metropolitan Area and the Algarve (9). Moreover, the number of unemployed individuals registered in 74 municipalities during April 2020 was more than twice the registered number in the same month of the previous year (9). However, and unlike the financial crisis of 2011, any interventions or measures toward cost containment of the health sector should be taken with great precaution. In the one hand, any budget cuts that may affect the health sector in the future will limit the ability of the already exhausted sector in functioning against any recurrent outbreak, given the high risk of COVID-19 outbreaks over recurrent or seasonal waves (10–12). On the other hand, the economic situation of the country, in light of lower economic growth rates, may limit further spending on health.

Accordingly, it is more important than ever to obtain an optimal balance between health and economic stability. This perspective aims to review possible flaws in the health sector and potential interventions which may help achieve this balance in Portugal. We also aim to provide measures that can help in mitigating the financial consequences of the COVID-19 on the health system and to provide recommendations that can contribute for containing any similar outbreak in the near future.

COVID-19 PANDEMIC IN PORTUGAL

The first cases diagnosed with COVID-19 disease in Portugal were reported on March 2, 2020, while the first death was recorded on March 16, 2020 (13, 14). Portugal has adopted several measures in order to contain the transmission of the virus and contain the expansion of the disease. First, on March 18, 2020, the state of emergency was declared in Portugal, through the Decree of the President of the Republic No. 14-A/2020 (15). The decree imposed extraordinary urgent measures in the form of restrictions over domestic and international movements and the application of social distancing rules. Moreover, and due to the unprecedented health crisis imposed by the pandemic, the country had approved a new decree that allows legal immigrants with pending residence application who applied for legal residence in the country until March 18, when the state of emergency was decreed, to have access to health care services during the pandemic (16). With the measure, immigrants will have access to the same rights as Portuguese citizens, including use of the health system and social and financial support from the government. The decision also benefits those who have applied for asylum. Second, and regarding surveillance capabilities, and as of June 3, 2020, the government has set a network of testing centers that consists of 205 laboratories distributed across the country (17). Most of these laboratories follow the National Health Service (SNS) (45.2%) and the private sector (39.3%), but they also include other laboratories, namely, the military and the academic laboratories (15.7%) (18, 19). In April 2020, the average number of tests was 11,500 tests per day, and in May 2020, the average was 13,550 tests per day (20). As of June 3, 2020, more than 860,000 tests have been carried out to detect the disease in Portugal (20). About 40% of the COVID-19 tests were conducted in the Norte region of the country, followed by Lisbon and Vale do Tejo (25%) and the Centro (14%) regions (20). The remaining statistics are distributed over the remaining regions. Areas dedicated to treat patients with COVID-19 were created through several selected Emergency Service Units (ADC-SU) and COVID-19 Community Dedicated Areas (ADC-COMMUNITY) (21). The selection of COVID-19 dedicated areas depended on several factors that included population density, geographical dispersion, and the regional and local epidemiological evolution of COVID-19 (21).

As of June 3, 2020, the number of confirmed cases of COVID-19 per 10,000 inhabitants was 32.6 (9). Despite the progressive spread of the pandemic throughout the country, its spread continues to be characterized by a high regional heterogeneity and affected by various socio-economic impacts (9). However, analyzing the spread of COVID-19 by local administrative unit (LAU 1) (22), also known as municipality level, it translates

into marked variation in the spread of the disease across municipalities. Portugal is divided into seven regions according to Nomenclature of Territorial Units for Statistics (NUTS II) (23) as follows: Norte, Centro, Lisbon Metropolitan Region (also known as Lisboa e Vale do Tejo), Alentejo, Algarve, Autonomous Region of the Azores, Autonomous Region of Madeira. The seven regions are divided into 308 LAU 1 or municipalities. The Norte region carries a substantial burden especially when taking into account the absolute numbers of confirmed cases and deaths due to COVID-19. As of June 3, 2020, the confirmed cases in the Norte regions accounted for 50.5% of total confirmed cases and 55% of the total number of deaths (24) (see Table 1 for an informative overview of epidemiological situation in Portugal). At the municipality level, the number of confirmed cases per 10,000 inhabitants was higher than the national average in 50 municipalities (9). Of these, 31 were located in the Norte region, especially the municipalities located in the Metropolitan Area of Porto with more than 50 confirmed cases per 10,000 inhabitants, 11 municipalities in the Centro region, five in the Lisbon Metropolitan Region (the municipalities of Loures, Amadora, Lisbon, Odivelas, and Sintra), two in Alentejo region (the municipalities of Moura and Azambuja), and one municipality in the Autonomous Region of the Azores (the municipality of Nordeste) (9). Moreover, of the 50 municipalities with a number of confirmed cases per 10,000 inhabitants above the national average, 10 also had values of new confirmed cases per 10,000 inhabitants above the national average in which half of these municipalities were located in the Metropolitan Area of Lisbon (9).

Moreover, 34 out of these 50 municipalities above the national level, almost two thirds, have a population density above the national average, and this highlights how population density can affect the spread of the disease (9). Of these 34 municipalities with population density above the national average, the highest number of confirmed cases per 10,000 inhabitants were recorded in the municipality of Ovar (123 cases per 10,000 inhabitants), while the lowest number were recorded in the municipality of Lisbon (52.1 cases per 10,000 inhabitants) (9).

MEASURES TO MITIGATE THE EFFECT OF COVID-19 IN PORTUGAL

Urgent Integration of Quality Indicators Within Hospitals Systems

Since we are encountering an unprecedented situation, immediate actions should be taken to preserve limited medical resources and prevent further unnecessary expenditure. Evidence from several countries suggest that unnecessary health spending, also known as wasteful spending, accounts for almost one-fifth of health expenditure in the form of unnecessary treatments or examinations, or health services provided with unnecessary higher costs (26, 27). Reducing or eliminating unnecessary health expenditure could be achieved without impairing quality of care (28). On the contrary, it will allow the health system to absorb an abrupt or unexpected increase in demand for medical resources, as in the case of COVID-19. As regards hospitals, hospitalizations or additional in-patient stays that consume a

TABLE 1 | The Epidemic of COVID-19 in Portugal by Regions as of June 3, 2020.

Portuguese Regions (NUTS II)	Norte	Centro	Lisbon	Alentejo	Algarve	Madeira	Azores
Number of confirmed cases, <i>N</i> (%)	16,804 (50.5)	3,765 (11.3)	11,828 (35.6)	260 (0.8)	378 (1.1)	90 (0.3)	138 (0.4)
Number of deaths, <i>N</i> (%)	796 (55.0)	240 (16.6)	380 (26.3)	1 (0.1)	15 (1.0)	0 (0.0)	15 (1.0)
Number of laboratory testing centers, <i>N</i>	51	49	62	12	12	-	-
Number of dedicated COVID-19 centers, <i>N</i>	54	24	27	13	3	-	-
Number of municipalities above the national average of confirmed cases ^a , <i>N</i> (%)	31	11	5	2	0	0	1
Distribution of COVID-19 tests by region (%)	40	14	25	-	-	-	-

Sources of data: Instituto Nacional de Estatística (INE) (9); Direção-Geral da Saúde (DGS) (1, 25); Serviço Nacional De Saúde (SNS) (20).

NUTS II Nomenclatura de Unidades Territoriais para Fins Estatísticos, nível II (Territorial Nomenclature Units for Statistical Purposes, level II); R.A. Região Autónoma (Autonomous Region).

^aNumber of cases per 10,000 inhabitants.

considerable amount of resources could be avoided with efficient treatment and management of chronic diseases, knowing that chronic diseases in Portugal consume a considerable amount of the health budget (29–34).

We pointed out, in previous contributions (30, 34), possible approaches to reduce the costs of healthcare in Portugal through integrating quality measures of hospitals' performance, namely thirty-day readmission rate and length of stay (LOS). Thirty-day hospital readmission is defined as an episode in which a patient is readmitted within 30 days from the last discharge. LOS is defined as the number of days a patient is hospitalized in relation to the admission diagnosis. High rates of thirty-day readmissions or unnecessary delayed discharge that contributes to higher LOS have been recognized as frequent and costly events (30, 35–37). For example, in the United States, one in five Medicare beneficiaries has a thirty-day readmission, with a cost of around \$26 billion per year (37, 38). Accordingly, these measures have been widely used as a quality benchmark for health systems (30, 39–44). Given the expected implications of COVID-19 on the Portuguese economy and the health sector, it is mandatory that policymakers adopt these measures to impact cost and quality through payment incentives for hospitals or health care providers. By integrating quality indicators in the Portuguese health sector, we can focus on other areas of improvement, as listed in the following sections:

Addressing Deficiencies in the Health System Infrastructure and Human Resources

The spread of COVID-19 created unprecedented pressure on hospitals and medical human resources, even in the most developed countries. With health system being stretched beyond its capacity, curative beds and critical care capacity require substantial review. Portugal has a total of 35,000 beds distributed between public, private, and public-private partnership hospitals; 22,400, 10,900, and 1,600, respectively (45). It is also important to mention that there was a decrease in the total number of beds over the period from 2007 to 2017 (45). For example, the total number of beds in 2017 was 84 beds lower than in 2016 and markedly lower than in 2007 with less 1,267 beds. This decline

is owed to the steady increase in day surgery, the reinforcement of the long-term care networks, mergers between public hospitals and the closing of psychiatric hospitals (46, 47). Overall, Portugal has a lower number of curative beds per 100,000 population (325.2) compared to other European countries (6, 46).

The number of active physicians certified by the Portuguese Medical Association was 53,657 in 2018 (48). In addition, the number of active nurses certified by the Portuguese Nurses Association was 73,650 in 2018 (48). An increasing trend in the number of doctors and nurses have been reported in the period from 1960 to 2018 (48), while a decreasing trend in the number of inhabitants per doctor and nurses have been reported for the same period (49). However, these seemingly positive trends should be interpreted with caution. First, Portugal has one of the lowest ratios of nurses per 100,000 population (638 per 100,000 population) when compared with the European Union (EU) average (864 per 100,000 population) (46, 50). Second, the economic crisis of 2011 has led to significant outflows of emigration among doctors and nurses working in Portugal seeking better salaries and working conditions (46). For instance, the period from 2011 to 2015 witnessed the emigration of 1,631 doctors and 12,680 nurses from Portugal according to data from the Portuguese Medical and Nursing Associations (46). While current concerns about the shortage of medical human resources in Portugal are valid and real, what is more alarming is how this shortage can affect any strategies to curb the current infection. Moreover, we should expect that this pandemic will put the developed countries in a rival for attracting healthcare workers due to shortage in medical human resources or giving the crucial value they have had during this crisis. Accordingly, it is more important than ever that the Portuguese government set an action plan to retain the current work forces and address any further shortages. Moreover, since the density of the population plays an important role in shaping the distribution of COVID-19, solutions should be provided to ensure the allocation of medical resources to the municipalities with high population density.

Addressing Health Inequalities in Portugal

Health inequalities can play an important role in shaping the distribution of COVID-19. Recent emerging data show the potential role of sex, race, and age on COVID-19

hospitalization and mortality rates, in which specific groups are disproportionately affected by the disease (51, 52). For example, the African-American community, which constitutes only 13% of the United States population, accounts for 33% of the hospitalizations related to COVID-19, while White Americans who constitute 76% of the total population account for 45% of the total hospitalizations (51). It is well-known that the African-American community in the United States carries a substantial burden when it comes to health inequalities with a higher risk of having a variety of health problems and less access to health care than White Americans (53–55). These findings are especially worrisome when considering how the apparent aspects of health inequalities can aggravate the COVID-19 distribution in Portugal. It is important to mention that socioeconomic characteristics are important indicators for health inequalities in Portugal (34, 56, 57). Portugal has a high proportion of elderly population, which is among the most affected by COVID-19, with those aged 65 years or more accounting for almost 20% of the total population (58). Table 2 shows the substantial effect of COVID-19 among the elderly population in Portugal in which infections among those aged above 60 years represent 32.7% of the total infections, while deaths among the same age group accounts for 95.4% of the deaths (1).

Migrants' health in Portugal illustrates another aspect of inequality, which translates into migrants using less and reporting more access restrictions (59). Although COVID-19 morbidities and fatalities by immigration status are not available yet, probably existing inequalities will be exacerbated in the present context. These expectations are supported by recent figures from the epidemiological bulletin of the Directorate-General for Health (DGS) indicating that municipalities located in the Metropolitan Area of Lisbon, which is characterized by having high migrants' concentrations, started to show a marked increase in the new cases per 10,000 inhabitants (1, 9). Over 50% of migrants are living in the Lisbon Metropolitan Area which is the home of 30% of the total Portuguese population (60). Also, it is important to know that municipalities with high concentrations of migrants record population density above the national level. For example, the municipality of Amadora, in the Metropolitan Area of Lisbon, which is known to have one of the largest migrant populations in the country, namely, in the neighborhood of The Bairro da Cova

da Moura, is recording the highest population density in the entire country with almost 8000 inhabitants per square kilometer (59), in comparison to the average national population density of 111.5 inhabitants per square kilometer (61). Moreover, the same municipality of Amadora, is currently recording the highest number of new confirmed cases per 10,000 inhabitants above the national average (11.1 new cases per 10,000 inhabitants), followed by municipalities in the same Metropolitan Area of Lisbon as follows: Loures (10.0), Odivelas (7.4), Sintra (5.8), and Lisbon (4.9), which are also known to have high concentrations of migrants. Also, the health authorities were obligated to take drastic measures in the form of closing restaurants, cafés, and bars in one of the poorest migrants' social neighborhood in the country "Vale de Chicharos," also known as "Bairro da Jamaica," to contain the spread of an outbreak of new cases detected among residents (62). These findings are alarming, given the strong evidence that migrants and ethnic minorities specifically carry a substantial burden when it comes to infectious diseases owing to the lack of access to preventive health services and information (63). Moreover, previous studies showed migrants are among the most affected by infectious diseases and epidemics during economic crises due to worsening living conditions and lack of access to healthcare and treatment (64). These concerns highlight the consequences of measures that do not ensure the full entitlement of migrants in the health system. Since the government allowed documented migrants full access to health care services, solutions should also be provided to guarantee undocumented migrants full access to healthcare services without bearing any financial or legal consequences, especially in the light of the increasing number of new confirmed cases in areas with high migrant concentrations. Undocumented migrants in Portugal have limited healthcare entitlements compared to documented migrants (59). This unprecedented public health crisis due to COVID-19 should emphasize that the exclusion of any vulnerable populations from health care could halt the fight against the spread of infection.

Another aspect of health inequality is the unequal geographical distribution of health services and human resources for health in Portugal. In Portugal, human resources for health, health equipment, and supplies are concentrated in Lisbon and Porto, when compared to the country's remote areas (46, 47). Moreover, relatively younger populations are concentrated in the country's coastal regions, which are well-known to have higher socio-economic positions and better access to health care services compared to the rest of the country (47, 65). On the contrary, residents of remote areas, with lower socio-economic indicators, have poor geographical access to health services, which influences their ability to utilize health care services (47). These facts are supported by the heterogeneous spread of the disease over the country. For example, the majority of municipalities that recorded confirmed cases above the national level were lock land municipalities (40 municipalities) against only 10 coastal municipalities (59). Our concern is that these aspects of inequalities will contribute to the spread of the disease in Portugal. These concerns demand interventions that guarantee a fair distribution of medical resources all over Portugal knowing that areas with relatively old Populations are more deprived of health services. Policies should also be developed to ensure the

TABLE 2 | Number of confirmed cases and deaths by age in Portugal as of June 3, 2020.

Age Groups	Confirmed Cases		Deaths	
	N	(%)	N	(%)
0–19	1,864	(5.6)	0	(0.0)
20–39	9,502	(28.6)	3	(0.2)
40–59	11,031	(33.2)	63	(4.8)
60–69	3,600	(10.8)	128	(8.8)
70–79	2,649	(8.0)	278	(19.2)
80+	4,615	(13.9)	975	(67.4)
Total	33,261	(100.0)	1,447	(100.0)

Sources of data, *Direção-Geral da Saúde (DGS)* (1).

full and sustainable inclusion of migrants in the national health system without bearing any financial or legal consequences.

Improving Mental Health Services

The increasing mortalities and morbidities due to COVID-19 made health care workers and general population to experience mental health problems such as depression and anxiety (66, 67). Moreover, the quarantine measures imposed to contain SARS-CoV-2 transmission that resulted in unprecedented social distancing and altered lifestyles began to have serious effects on mental health (68, 69). We might also expect (these associations tend to worsen) seeing similar effects as rates of unemployment, job loss, and poverty due to the economic effect of COVID-19 are increasing. For instance, during the economic crisis of 2011, Portugal witnessed a similar situation in which there was a surge in mental health problems (70, 71). In fact, the associations between the implications of economic crisis, such as unemployment or poverty, and mental health problems are well-documented (24).

These findings may be deemed worrying given the weaknesses and unpreparedness of the mental health services in Portugal to respond to such sharp demand. In the last decade, Portugal has witnessed a decrease in the number of psychiatric beds in favor of promoting community-based mental health services (28). However, a recent assessment of the Portuguese mental health plan indicated that country is still far from obtaining this goal (72). Also, it is important to know that that mental health in Portugal is lagging, compared to other European countries, in terms of the high prevalence of mental problems and the development of community-based mental health services (73, 74). Despite this fact, only a small proportion of patients who have mental illness have access to public specialized mental health services (73). In addition, mental health services in Portugal have substantial insufficiencies regarding equity and quality of care (73), given the substantial cost of mental health illness in EU in general, which is estimated to account for more than 4% of GDP (28). Portugal should put in place policies to address mental health among the population in general and to ensure emergency access to treatment for individuals affected by COVID-19 through establishing procedures for psychological crisis interventions.

Preparedness Is the Key

If there is one lesson to be learned from the COVID-19 pandemic, it will be how to advance preparedness in other countries to mitigate the effect of the outbreak, and this should be instructive for Portugal. Taiwan and Singapore's response to the COVID-19 has been considered as a model, thanks to the SARS outbreak in 2003. These countries were among the most affected ones during the SARS outbreak (75–77). However, afterwards, they have established and developed their outbreak preparedness policies (75, 77). These policies included developing a public health action plan for facilitating rapid responses for the following crisis, holding regular exercises, establishing a central command center for epidemics, and building new infrastructures equipped with hundreds of negative-pressure isolation rooms and public health preparedness clinics (77, 78). As a result, they were able

to successfully mitigate and contain the virus spread and keep it under control. Given this success and in light of the devastating implications of COVID-19, understanding and adopting the strategies implemented in these countries and their effectiveness may enlighten health policymakers in Portugal. As a starting point, an urgent public health response plan for allowing rapid actions for any possible future outbreak should be established in Portugal. This plan should include strategies to address shortages in human or medical resources or any flaws in the health system infrastructures. Hospitals also need guidelines to manage their spaces, human resources, and supplies to be able to contain any future similar outbreaks. Any plans should also consider reviewing the number and distribution of ventilators in the country, which is critical in treating severely ill patients. Moreover, specific specialties should be the focus of significant investment; for example, anesthesiologists, radiologists, and emergency room physicians should have particular skills that make them notably valuable to treat severely ill COVID-19 patients. The plan should also target the deficiencies in specialties such as public health doctors, which represent only 1.5% of the total active doctors in Portugal (46), and medical disaster specialists.

The health sector in Portugal can be more efficient in order to increase its ability to absorb any similar outbreaks by achieving that we can work on improving different aspects within the health sector by allocating resources, addressing shortage in medical and human resources. This unprecedented situation imposed the fact that public health cannot be achieved anymore without addressing health inequalities especially among migrant populations. The absence of a treatment or vaccine for COVID-19 should not be considered an excuse for the lack of national strategies and actions to contain and mitigate the effect of the current pandemic or any future similar outbreaks that pose an unprecedented threat to public health and the economy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AS conceived the work, reviewed literature, and wrote the manuscript. BP and MM supervised the work and wrote the manuscript. All authors have agreed on the final version of the manuscript.

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Paper III



Risk of Readmission Among HIV Patients in Public Portuguese Hospitals: Longitudinal Multilevel Population-Based Study

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Background: Thirty-day hospital readmission is receiving growing attention as an indicator of the quality of hospital care. Understanding factors associated with 30-day hospital readmission among HIV patients in Portugal is essential given the high burden cost of HIV hospitalizations in Portugal, a country suffering from financial constraints for almost 10 years.

Objectives: We aimed to estimate the 30-day hospital readmission rates among HIV patients in Portugal and to identify its determinants using population-based data for Portuguese public hospitals.

Study Design: A multilevel longitudinal population-based study.

Methods: Between January 2009 and December 2014, a total of 37,134 registered discharges in the Portuguese National Health Service (NHS) facilities with HIV/AIDS as a main or secondary cause of admission were analyzed. Logistic regression was used to compare 30-day hospital readmission categories by computing odds ratio (OR) and corresponding 95% confidence intervals (95% CIs). A normal random effects model was used to determine unmeasured factors specific to each hospital.

Results: A total of 4914 (13.2%, 95% CI: 12.9%–13.6%) hospitalizations had a subsequent 30-day readmission. Hospitalizations that included exit against medical opinion (OR = 1.18, 95% CI: 1.01–1.39), scheduled admissions (OR = 1.71, 95% CI: 1.58–1.85), and tuberculosis infection (OR = 1.20, 95% CI: 1.05–1.38) exhibited a higher risk of hospitalizations with subsequent 30-day readmission. In contrast, hospitalizations that included females (OR = 0.87, 95% CI: 0.81–0.94), a transfer to another facility (OR = 0.78, 95% CI: 0.67–0.91), and having a responsible financial institution (OR = 0.63, 95% CI: 0.55–0.72) exhibited a lower risk of hospitalizations with subsequent 30-day readmission. Hospitalizations associated with higher number of diagnosis, older ages, or hospitalizations during the economic crisis showed an increasing trend of 30-day readmission, whereas an opposite trend was observed for hospitalizations with higher

number of procedures. Significant differences exist between hospital quality, adjusting for other factors.

Conclusion: This study analyzes the indicators of 30-day hospital readmission among HIV patients in Portugal and provides useful information for enlightening policymakers and health care providers for developing health policies that can reduce costs associated with HIV hospitalizations.

Keywords: HIV/AIDS, quality of care (measurement), 30-day readmission, hospital performance indicators, random effects model

INTRODUCTION

Thirty-day readmission rate has obtained a growing attention as a benchmark indicator for measuring hospital's quality and hospital's performance (1–7). However, although previous studies have recognized hospitalizations with subsequent 30-day readmission as a cost-driving cause and as a cause for frequent problems among people living with HIV (7), there remains a scarcity of research pertaining to the factors associated with readmissions rates, especially when it comes to assessing readmission among HIV patients in Portugal. Admissions among HIV patients still pose considerable challenges to the Portuguese health system. In general, and despite the significant health reforms in Portugal in recent decades (8), HIV infection continues to be a main public health concern (9–11). In Portugal, costs associated with HIV/AIDS hospitalizations represent a substantial economic burden, ranked as the second major diagnosis category (12). In addition, and after the financial crisis that hit the country in 2011, Portugal was obligated to sign up for a bailout program from several funding entities including the European Central Bank and the IMF (13). As a result, the country went through strict fiscal austerity that resulted in budget cuts, reduction of spending on sensitive health sectors, and restructuring numerous public entities including the National AIDS Program (NAP) (12–15). Given these unfavorable economic conditions, and the strains on the Portuguese's health care system with the growing demands on health care resources, it is more important than ever to integrate efficiency measures to maximize the benefits given the available resources. A best-practice readmissions target is fewer 30-day readmission rates, and fewer differences in the care provided among hospitals, without affecting the clinical outcomes for the patients admitted to the hospital and without increasing allocated resources. Since the Portuguese government set the policy of cost reduction as a target to stabilize the economic situation, a considerable work should be devoted to controlling the factors and indicators that tend to push readmission expenses further. Accordingly, this study aims to describe and analyze factors associated with the subsequent 30-day readmission among HIV patients in Portugal by applying ordinary and multilevel logistic regression models to 30-day readmission outcomes in order to compare the two methods with the focus on the interpretation of hospital-level risk factors and to identify differences in hospital quality for the period 2009–2014.

METHODS

Study Design

We used a longitudinal multilevel population-based study. Data are arranged in a natural hierarchy as in the context of patients-in-hospitals two-level data. Patients within a given hospital typically tend to be more alike than patients across different hospitals in measured and unmeasured characteristics predictive of outcome (16). Accordingly, a multilevel logistic regression model is appropriate to consider the impact of risk factors on readmissions while adjusting for variations in hospitalizations and hospital characteristics (16, 17). Disregarding the clustering present in multilevel data results in an inflated number of independent observations at the hospital level of the hierarchy, and accordingly will underestimate the magnitude of the effect of hospital-level's standard error as occurs in ordinary logistic regression (16). The different empirical models estimated are explained in the *Statistical techniques*.

Data Collection and Source

The present analysis is based on data collected as part of the national registered discharges among the Portuguese National Health Service (NHS) facilities. We reviewed hospitalization records for all HIV/AIDS patients admitted in Portugal, between 1st January, 2009, and 31st December, 2014, in 48 hospitals in Portugal. These data are anonymous, refer to the DRGs, and were obtained through the Central Health System Administration (ACSS) (18). Each record corresponds to a discharge episode and contains information collected while the patients were admitted to the hospital.

Study Participants

A total of 37,134 discharges among patients aged 18 years or older were included in the study. For the purpose of this study, data about discharges with HIV/AIDS as a main or secondary cause of admission, [ICD-9, 042, V08], were analyzed. In addition, readmission episodes and the time span between the readmission and the last discharge were calculated. Primary and secondary diagnoses and procedures were coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Nineteen secondary diagnoses and up to 20 procedures were considered in this study.

Variables

The main outcome is 30-day readmission. To determine 30-day readmission rate, we used a unique fictional code included in

the data that allows determining how many episodes correspond to the same user, in the same institution. This fictional code does not identify the user or allow its identification afterward. Accordingly, readmission episodes and the time span between the readmission and the last discharge were calculated. Our main outcome was created as follows: $Y = 0$ if hospitalizations without subsequent 30-day readmission, $Y = 1$ if hospitalizations with subsequent 30-day readmission(s).

We considered the following independent variables: demographic characteristics (age, sex, insurance), index hospitalization [admission type (urgent or scheduled), type of intervention (surgical or not), diagnoses and procedures (number of diagnoses, number of procedure), associated TB Infection (yes or no)], and prior health care utilization (mode of transfer, destination after discharge). Since several hospitals have been merged in one hospital during the period between 2009 and 2014, we created a dummy variable (hospital merge dummy) to categorize hospitals according to the merging status (Yes: merged, No: Not merged) to be able to study the effect of merging on hospital quality.

Statistical Analysis

We used the Pearson chi-squared test to compare nominal variables, and the non-parametric tests for ordinal variables. Univariate and multivariate logistic models were estimated to identify the determinants of hospitalizations with subsequent 30-day readmission. Odds ratio (OR) and corresponding 95% confidence intervals (95% CIs) were calculated. For the multilevel approach, a binomial random effects model with a logit link function was used to study the relationship between independent variables and the main outcome. A normal random effect for the hospitals was included and should be interpreted as differences in hospital quality/performance. Multiple comparisons of hospital effects were done by constructing 95% CIs for random effects. All analyses were conducted with STATA®, version 11.2 (StataCorp LP, College Station, Texas, USA), and RStudio, namely the library MASS.

Statistical Techniques

First, ordinary crude and adjusted logistic regression models (16, 19) were applied to assess the influence of risk factors on 30-day readmission. If we assume that p_{ij} is the probability and $\frac{p_{ij}}{1-p_{ij}}$ is the odds of readmission for hospitalization j in hospital i , the specification and the equation of the ordinary logistic model is as follows:

$$\log \left(\frac{p_{ij}}{1-p_{ij}} \right) = \beta_0 + \sum_{k=1}^R \beta_k X_{ijk} \quad (1)$$

where the X_{ijk} 's represent a patient's values of R risk factors, and $\beta_1 \dots \beta_R$ are regression coefficients corresponding to each risk factor. For a given risk factor, its coefficient β_k is the log OR comparing the effect on 30-day readmission of the risk factor's presence with its absence (16), if a risk factor is an indicator, for example, of associated TB infection (1 if yes, 0 if no). Exponentiating β_k (e^{β_k}) gives the corresponding OR. In ordinary logistic regression, hospital characteristics are

treated the same as hospitalization-level risk factors (16), and hospitalization independent variable Y_{ij} is a binomial variable with 30-day readmission probability p_{ij} .

Multilevel logistic regression (16, 20) assumes that each hospital has its own underlying 30-day readmission probability and this varies from hospital to hospital. In this multilevel model, the logistic regression for 30-day readmission includes an additional term, u_i , which is the hospital-level random effects as a predictor variable:

$$\log \left(\frac{p_{ij}^*}{1-p_{ij}^*} \right) = u_i + \beta_0 + \sum_{k=1}^R \beta_k X_{ijk} \quad (2)$$

In this model, p_{ij}^* is the probability that hospitalization j in hospital i will be readmitted within 30 days of the last discharge. The probability depends on the value of the random effects, u_i , for that hospital (16). u_i is the totality of measured and unmeasured hospital-level variables that predict 30-day readmission and are uncorrelated with the individual and hospital-level predictor variables in the model. Accordingly, u_i represents the combination of omitted hospital-level variables (16).

Variation in 30-day readmission propensity between hospitals is accommodated by assuming a normal distribution for u_i with mean zero and variance τ^2 . A hospital with $u_i = 1$ can be thought of as having "average" (compared to other hospitals in the population) 30-day readmission probability (on the log odds scale). Higher values of τ^2 indicate greater heterogeneity in 30-day readmission among hospitals included. By incorporating the u_i term in the model as a random effects, the interdependencies among hospitalizations within hospitals are considered (16, 20). Hospital case-mix index (CMI) from B to F had been combined with all hospitals included in our study. CMI reflects the clinical complexity of a particular inpatient population in a medical care environment, and it measures the relative costs and resources needed to treat this inpatient population (21). In our study, hospitals with CMI B are considered receiving patients in less complicated conditions while hospitals with CMI E are considered receiving patients in worst conditions. Group F refers to hospitals treating specific diseases, such as oncological institutes.

We included a prediction model by measuring the area under the Receiver Operating Characteristics curve (AUC-ROC). AUC-ROC curve is a performance measurement for classification problem at various thresholds settings. ROC is a probability curve and AUC represents degree or measure of separability. The curve indicates the ability of the model in distinguishing between classes. In logistic regression, the higher the AUC, the better the model is at discriminating between discharges with and without 30-day readmissions.

RESULTS

Between 1st January 2009 and 31st December 2014, there were 37,134 registered discharges in the Portuguese NHS facilities with HIV/AIDS as a main or secondary cause of

TABLE 1 | Characteristics of the hospitalizations according to the main outcome: $Y = 0$ if hospitalizations without subsequent 30-day readmission, $Y = 1$ if hospitalizations with subsequent 30-day readmission(s).

	All hospitalizations		Hospitalizations without subsequent 30-day readmission		Hospitalizations with subsequent 30-day readmission		P-value
	N	%	N	%	N	%	
Sex n (%)							
Men	25,060	67.5	21,485	66.7	3,575	72.8	<0.001
Women	12,074	32.5	10,735	33.3	1,339	27.2	
Admission type n (%)							
Urgent	25,818	69.53	22,793	70.74	3,025	61.56	<0.001
Scheduled or others	11,316	30.47	9,427	29.26	1,889	38.44	
Associated TB infection n (%)							
No	35,204	94.80	30,579	94.91	4,625	94.12	<0.05
Yes	1,930	5.20	1,641	5.09	289	5.88	
Mode of transfer n (%)							
No transfer	33,341	89.79	28,791	89.36	4,550	92.59	<0.001
Transfer to other facility ^a	3,793	10.21	3,429	10.64	364	7.41	
Responsible financial institution SNS n (%)							
No	1,711	4.61	1,262	3.92	449	9.14	<0.001
Yes	35,423	95.39	30,958	96.08	4,465	90.86	
Destination after discharge n (%)							
Home	30,452	82.01	26,486	82.20	3,966	80.71	<0.001
To another institution with hospitalization	1,793	4.83	1,652	5.13	141	2.87	
Exit against medical advice	1,284	3.46	1,083	3.36	201	4.09	
Deceased	3,230	8.70	2,687	8.34	543	11.05	
Special service ^b	375	1.01	312	0.97	63	1.28	
Year n (%)							
2009	6,200	16.70	5,468	16.97	732	14.90	<0.001
2010	6,259	16.86	5,515	17.12	744	15.14	
2011	6,684	18.00	5,743	17.82	941	19.15	
2012	6,715	18.08	5,726	17.77	989	20.13	
2013	6,689	18.01	5,734	17.80	955	19.43	
2014	4,587	12.35	4,084	12.52	553	11.25	
Age n (%)							
18–25	938	2.5	855	2.7	83	1.7	<0.001
26–35	6,650	17.9	5,739	17.8	911	18.5	
36–45	13,357	36.0	11,607	36.0	1,753	35.7	
46–55	8,369	22.5	7,256	22.5	1,113	22.7	
≥55	7,820	21.1	6,766	21.0	1,054	21.5	
Number of diagnosis n (%)							
Median (IQR)	6 (4-8)		6 (4-8)		6.5 (4-9)		<0.001
≤=4	13,203	35.56	11,743	36.45	1,460	29.71	<0.001
5–6	8,653	23.30	7,656	23.76	997	20.29	
7–8	6,202	16.70	5,150	15.98	1,052	21.41	
>8	9,076	24.44	7,671	23.81	1,405	28.59	
Number of procedure n (%)							
Median (IQR)	6 (3-9)		6 (3-10)		5 (2-8)		<0.001
≤=3	11,615	31.28	9,757	30.28	1,858	37.81	<0.001
4–6	8,950	24.10	7,738	24.02	1,212	24.66	
7–9	7,485	20.16	6,608	20.51	877	17.85	
>9	9,084	24.46	8,117	25.19	967	19.68	

(Continued)

TABLE 1 | Continued

	All hospitalizations		Hospitalizations without subsequent 30-day readmission		Hospitalizations with subsequent 30-day readmission		P-value
	N	%	N	%	N	%	
Type of intervention n (%)							<0.001
Surgical	8,689	23.40	8,018	24.89	671	13.65	
Medical or others	28,445	76.60	24,202	75.11	4,243	86.35	
Hospital merge dummy							0.001
No	23,470	63.20	20,468	63.53	3,002	61.09	
Yes	13,664	36.80	11,752	36.47	1,912	38.91	

CI, confidence interval; OR, odds ratio; RE, random effects.

*Transfer for conducting exams or follow-up or lack of resources or treatment of associated condition.

^bSpecial service includes home service, specialized aftercare, palliative care, and long-term hospital care.

admission. Table 1 presents the univariate analysis and the main characteristics of participants, according to readmission status. A total of 32,220 (86.8%, 95% CI: 86.4–87.1%) of the admissions were hospitalizations without subsequent 30-day readmission(s), while 4,914 (13.2%, 95% CI: 12.9–13.6%) were hospitalizations with subsequent 30-day readmission(s). Among the total admissions, 25,060 (67.5%) hospitalizations were recorded among males. The median age was 44 years with interquartile range between 37 and 52 years. Among individuals with subsequent 30-day readmission(s), there was a higher proportion of subjects with no financial institution when compared to subjects without subsequent 30-day readmission, 9.1 and 3.9%, respectively. The urgent admission was the main type of admission in both groups, 70.7 and 61.6%, respectively. Hospitalizations with subsequent 30-day readmission(s) presented the lowest proportion of subjects having surgical interventions (13.7 vs. 24.9%). In addition, the same category presented a higher proportion of exit against medical advice (AMA) in comparison with the other group (4.1 vs. 3.4%).

Table 2 presents the ordinary crude and adjusted logistic regression models and the multivariate logistic regression with random effects for the dependent variable $Y = 1$ if readmitted, $Y = 0$ if not. In the random effects model, and in comparison to males, females were less likely to have 30-day readmission episode, holding all other variables constant (OR = 0.87, 95% CI: 0.81–0.94). Scheduled admissions were more likely to be associated with <30-day readmission episode when compared to urgent admissions in the adjusted random effects model (OR = 1.71, 95% CI: 1.58–1.85). Moreover, admissions associated with TB infection were more likely to have subsequent 30-day readmission risk (OR = 1.20, 95% CI: 1.05–1.38) in the adjusted random effects model. Admissions associated with a transfer to another hospital/facility for conducting exams or follow-up or lack of resources or treatment of associated condition were less likely to be readmitted (OR = 0.78, 95% CI: 0.67–0.91) in the ordinary adjusted model. Regarding types of discharge, hospitalizations of patients who exit against medical opinion exhibited a pattern of increasing readmission risk (OR = 1.18,

95% CI: 1.01–1.39) in the random effects model. In addition, admissions associated with patients who deceased later were more likely to be readmitted in the random effects model (OR = 1.47, 95% CI: 1.32–1.64). The opposite is seen in admissions followed by discharged to another institution with hospitalization (OR = 0.61, 95% CI: 0.46–0.80). As regards the year of readmission, admissions in 2011 were more likely to have subsequent 30-day readmission following hospital discharge when compared with 2009 in the crude (OR = 1.22, 95% CI: 1.10–1.36), ordinary adjusted (OR = 1.15, 95% CI: 1.03–1.28), and adjusted with random effects model (OR = 1.13, 95% CI: 1.02–1.27). In addition, admissions occurred in the year 2012 showed the same pattern in the crude (OR = 1.29, 95% CI: 1.16–1.43) and the ordinary adjusted models (OR = 1.14, 95% CI: 1.03–1.27). However, there was a significant decrease in the likelihood of subsequent 30-day readmission in the admissions occurred in 2014 in the ordinary adjusted (OR = 0.70, 95% CI: 0.62–0.80), and the adjusted model with random effects (OR with RE = 0.74, 95% CI: 0.65–0.85). Individuals who have a responsible financial institution (SNS) were less likely to have 30-day readmission (OR = 0.63, 95% CI: 0.55–0.72) in the random effects model. All categories of older ages in the ordinary crude model 26–35 (OR = 1.64, 95% CI: 1.29–2.07), 36–45 (OR = 1.56, 95% CI: 1.23–1.96), 46–55 (OR = 1.58, 95% CI: 1.25–2.00), ≥55 (OR = 1.60, 95% CI: 1.27–2.03) showed a significant increase in the likelihood of readmission risk, when compared to patients aged between 18 and 25 years old. Increasing readmission risk was consistently seen with progressively higher number of diagnosis 5–6 (OR = 1.21, 95% CI: 1.12–1.33), 7–8 (OR = 1.61, 95% CI: 1.46–1.78), >8 (OR = 2.13, 95% CI: 1.92–2.36). The opposite is seen in hospitalizations with progressively higher number of procedures 4–6 (OR = 0.82, 95% CI: 0.75–0.90), 7–9 (OR = 0.62, 95% CI: 0.56–0.69), >9 (OR = 0.47, 95% CI: 0.42–0.52), in which higher number of procedures was significantly less likely associated with 30-day readmission risk. Admissions associated with medical interventions were more likely to be followed by a 30-day readmission episode in comparison to admissions associated with surgical interventions (OR = 2.24, 95% CI: 2.034–2.46). The area under ROC curve that reflects the ability of our model to correctly

TABLE 2 | Logistic regression for the main outcome: $Y = 0$ if hospitalizations without subsequent 30-day readmission, $Y = 1$ if hospitalizations with subsequent 30-day readmission(s) using GLM with random effects.

	Constitutional ratio of 30-day readmission % (95% CI)	Crude OR (95% CI)	Adjusted OR without RE (95% CI)	Adjusted OR with RE (95% CI)
Sex				
Men	14.3 (13.8–14.7)	1	1	1
Women	11.1 (10.5–11.7)	0.75 (0.70–0.80)	0.83 (0.78–0.89)	0.87 (0.81–0.94)
Admission type				
Urgent	11.7 (11.3–12.1)	1	1	1
Scheduled or others	16.7 (16.0–17.4)	1.51 (1.42–1.61)	1.84 (1.71–1.99)	1.71 (1.58–1.85)
Associated TB infection				
No	13.1 (12.8–13.5)	1	1	1
Yes	15.0 (13.4–16.6)	1.16 (1.02–1.32)	1.12 (0.98–1.28)	1.20 (1.05–1.38)
Mode of transfer				
No transfer	13.6 (13.3–14.0)	1	1	1
Transfer to other facility ^a	10.0 (8.7–10.5)	0.67 (0.60–0.75)	0.78 (0.67–0.91)	0.98 (0.79–1.20)
Responsible financial institution SNS				
No	26.2 (24.2–28.3)	1	1	1
Yes	12.6 (12.3–13.0)	0.40 (0.36–0.45)	0.48 (0.42–0.54)	0.63 (0.55–0.72)
Destination after discharge				
Home	13.0 (12.6–13.4)	1	1	1
To another institution with hospitalization	7.9 (6.6–9.1)	0.57 (0.48–0.68)	0.74 (0.59–0.93)	0.61 (0.46–0.80)
Exit against medical advice	15.7 (13.7–17.6)	1.24 (1.06–1.45)	1.14 (0.97–1.34)	1.18 (1.01–1.39)
Deceased	16.8 (15.5–18.1)	1.35 (1.22–1.49)	1.44 (1.30–1.60)	1.47 (1.32–1.64)
Special service ^b	16.8 (13.0–20.6)	1.35 (1.03–1.77)	1.35 (1.02–1.79)	1.23 (0.92–1.64)
Year				
2009	11.8 (11.0–12.6)	1	1	1
2010	11.9 (11.1–12.7)	1.00 (0.90–1.12)	0.99 (0.88–1.10)	0.99 (0.88–1.10)
2011	14.1 (13.2–14.9)	1.22 (1.10–1.36)	1.15 (1.03–1.28)	1.13 (1.02–1.27)
2012	14.7 (13.9–15.6)	1.29 (1.16–1.43)	1.14 (1.03–1.27)	1.01 (0.98–1.23)
2013	14.3 (13.4–15.1)	1.24 (1.12–1.38)	1.04 (0.93–1.16)	0.98 (0.88–1.10)
2014	12.1 (11.1–13.0)	1.02 (0.91–1.15)	0.70 (0.62–0.80)	0.74 (0.65–0.85)
Age				
18–25	8.8 (7.0–10.7)	1	1	1
26–35	13.7 (12.9–14.5)	1.64 (1.29–2.07)	1.37 (1.07–1.74)	1.26 (0.99–1.61)
36–45	13.1 (12.6–13.7)	1.56 (1.23–1.96)	1.14 (0.90–1.45)	1.09 (0.86–1.39)
46–55	13.3 (12.6–14.0)	1.58 (1.25–2.00)	1.17 (0.92–1.49)	1.17 (0.92–1.49)
≥55	13.5 (12.7–14.2)	1.60 (1.27–2.03)	1.14 (0.90–1.46)	1.16 (0.91–1.48)
Number of diagnosis				
≤4	11.1 (10.5–11.6)	1	1	1
5–6	11.5 (10.8–12.2)	1.05 (0.96–1.14)	1.25 (1.14–1.36)	1.21 (1.12–1.33)
7–8	17.0 (16.0–17.9)	1.64 (1.51–1.79)	1.88 (1.72–2.07)	1.61 (1.46–1.78)
>8	15.5 (14.7–16.2)	1.48 (1.36–1.59)	2.20 (2.00–2.42)	2.13 (1.92–2.36)
Number of procedure				
≤3	16.0 (15.3–16.7)	1	1	1
4–6	13.5 (12.8–14.3)	0.82 (0.76–0.89)	0.76 (0.69–0.82)	0.82 (0.75–0.90)
7–9	11.7 (11.0–12.4)	0.70 (0.64–0.76)	0.57 (0.52–0.63)	0.62 (0.56–0.69)
>9	10.6 (10.0–11.3)	0.62 (0.58–0.68)	0.43 (0.39–0.48)	0.47 (0.42–0.52)
Type of intervention				
Surgical	7.8 (7.2–8.3)	1	1	1
Medical or others	14.9 (14.5–15.3)	2.09 (1.92–2.28)	2.52 (2.30–2.77)	2.24 (2.03–2.46)
Hospital merge dummy				
No	12.8 (12.4–13.2)	1	1	1
Yes	14.0 (13.4–14.6)	1.11 (1.04–1.18)	1.09 (1.02–1.16)	1.17 (0.84–1.65)

CI, confidence interval; OR, odds ratio; RE, random effects.

^aTransfer for conducting exams or follow-up or lack of resources or treatment of associated condition.^bSpecial service includes home service, specialized aftercare, palliative care, and long-term hospital care.

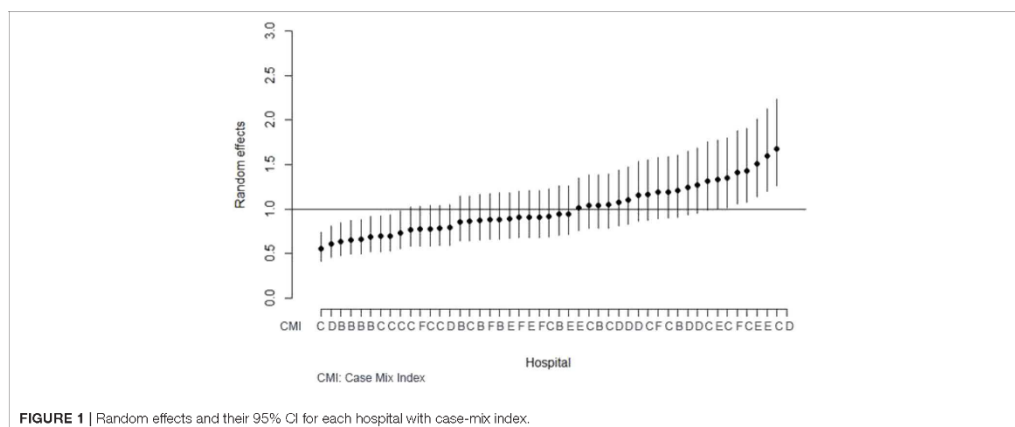


FIGURE 1 | Random effects and their 95% CI for each hospital with case-mix index.

classify discharges with and without 30-day readmission is 0.65 (95% CI: 0.65–0.66).

Figure 1 shows the random effects model for 48 hospitals included in the analysis that was used to determine unmeasured and unobserved factors specific to each hospital with their respective 95% CI. The random effects have been conducted as follows: $RE < 1$ means that the hospital is with more quality when compared to the mean, $RE > 1$ means that the hospital is with less quality when compared to the mean. The first nine hospitals have random effects and respective 95% CI below 1, being considered with more quality when compared to the mean, while the last seven hospitals' random effects exhibit higher likelihood of readmissions (random effects and corresponding 95% CI above 1). The same figure is combined with hospital's CMI from B to F. The figure shows that hospitals with less quality (more 30-day readmissions) have CMI classified by C, D, E, or F, meaning they receive patients in worse conditions when compared to the rest of the hospitals included in our study, while hospitals with better quality (less 30-day readmissions) present a lower CMI, meaning they receive patients in a less complicated condition: B, C, or D.

DISCUSSION

The purpose of this study was to estimate the rate of 30-day hospital readmission among HIV patients and to analyze its determinants using the Portuguese national admissions data. The estimated 30-day hospital readmission rate was 13.2% (95% CI: 12.9–13.6%). The results show variability in the patterns of readmission between hospitalizations with and without subsequent 30-day readmission(s). Our study identified increased comorbidity, the absence of a responsible financial institution, age, year of admission and exit against medical opinion as risk factors for of subsequent 30-day readmission. The 30-day readmission rate of 13.2% is almost similar to a study conducted in Brazil (6) and less than the rate of

19.3% reported by a similar study in the United States (1). This lower rate is less surprising if we consider the universal health coverage in Portugal in which all residents have access to health care provided by the NHS (9, 22). Portugal created the NHS to achieve greater equity of access to health care (23).

Our results showed differences in the risk of readmission between years. A significant increase in the likelihood of readmission was noticed after 2009 except for 2014. This finding can be explained by the economic crisis that led to cutting funds to several sectors including health and, as a result, compromising the quality of care (14). In addition, payments to NHS hospitals during the crisis have been reduced, including reduction for payments for in-patient's admissions, day cases, and consultations (24). This reduction was most probably associated with a decrease in hospitals' efficiency and quality by shortening the length of stay, decreasing the number of admissions, or by replacing in-patient admissions by day cases in an attempt to compensate for the effects of the new austerity measures (24). A previous study aimed to analyze the impact of the financial crisis on hospital care use in Portugal on some indicators including the rate of discharges per 100,000 habitants, and the in-patient length of stay (LOS) found the LOS to be significantly shorter with a higher rate of discharges per 100,000 after the crisis onset (24). However, The significant decrease in 30-day readmissions in 2014 is due to the ongoing process of reforming of the hospital sector in Portugal as part of the National Targets for Hospitals Reorganization that included eight initiatives (25). This reforming process started in 2011 in which each hospital should be committed to a 3-year action plan for hospital reorganization with the Regional Health Authority so that reform implementation can be continuously monitored by regional authorities (25). The results of these reforms have been found to positively affect quality and efficiency levels. The outcomes of these reforms have improved several quality measures including a marked reduction in readmissions rates (25).

Adjusted for other variables, admissions for patients not having responsible financial institution were found to increase the possibility of subsequent 30-day readmission risk. These results were in contrast to a previous study in the United States in which individuals who have no insurance were less likely to have 30-day readmission (1). One possible explanation for that could also be the difference in the health insurance system between the two countries. While both uninsured patients in Portugal and the United States have less access to the health services, as regards inpatient and follow-up services, those patients in Portugal can still be admitted to the hospitals through the emergency department without bearing any out-of-pocket payments. In contrast, the association between having no responsible financial institution and lower readmission rate in the United States can be interpreted by the economic barriers to seeking any medical care, including emergency admission, among uninsured patients (1, 26).

Compared to females, males had a higher risk of hospitalizations with subsequent 30-day readmission. When it comes to HIV in Portugal, it is well-known that men carry a disproportionately high burden of the disease. In 2011, the official data show a disproportionate disparity in both the prevalence rates of HIV infection and the mortality rates for deaths by an AIDS-related illness among men in Portugal, 73.6 and 83.9% subsequently (20, 22). In general, this finding can be explained by the fact that men are less likely to seek medical care and to demonstrate suffering or pain (27, 28), which may influence their experiences of living with HIV. In particular, men in Portugal demonstrate more ill health-related conditions throughout their lives as regards alcohol or drug use, unsafe sex, and engagement in risk behaviors than women, which can also be linked to this disproportionate pattern (29). The high rate of subsequent 30-day readmission among males in Portugal requires further investigation and this disparity requires strategies that aim to explain the role of gender and its influence on readmissions among HIV patients in Portugal.

Older ages exhibited patterns of increasing subsequent 30-day readmission risk. Our findings are consistent with previous studies that showed age as a risk factor for morbidity (30, 31), mortality (32, 33), and subsequent 30-day readmission (34) among individuals living with HIV. A possible interpretation for this finding is that age has a significant impact on the pattern of comorbid conditions associated with HIV (35, 36). In addition, and although antiretroviral treatment (ART) had contributed to a substantial increase in life expectancy among individuals living with HIV (37), long-term exposure to these medications may result in antiretroviral toxicity that may contribute to comorbidity (36). It is important to mention that previous studies that examined the interaction between HIV and age showed that some chronic medical conditions are related to antiretroviral toxicity (38, 39). Medicare, which is the federal health insurance program for people who are 65 or older in the United States, found that around 20% of Medicare beneficiaries have subsequent 30-day readmission, and these premature readmissions cost the American public around \$15 billion per year (40). This compelling evidence regarding age as a risk for comorbidity and subsequent readmissions demands the

inclusion of treatment protocols that guarantee a healthier older age among HIV patients.

Higher number of associated diagnosis exhibited a pattern of increasing readmission risk in our study. A study on the risk factors for all-cause hospital readmission within 30 days of hospital discharge found comorbidity as a strong risk factor for readmission in a general population of patients discharged from the hospital (3). In addition, several studies on the increased 30-day hospital readmission rates, specifically among HIV patients, appointed multiple comorbid chronic conditions as one of the major risk factors for premature readmission (4, 29). This finding supports the evidence that comprehensive care addressing multiple comorbidities is mandatory to decrease readmissions risk among HIV patients.

Leaving hospitalization AMA was also significantly associated with an increase in the rate of 30-day readmission. Leaving hospital AMA will lead to premature discharge, which is most probably associated with multiple readmissions due to uncompleted medical care. This finding is in accordance with previous studies that found a significant positive association between leaving hospital AMA and 30-day readmission (3, 18). Understanding the determinants of leaving the hospital AMA is of paramount importance to be able to identify possible predictors, and potential intervention for AMA, which is a crucial step toward curbing the premature readmissions among HIV patients.

Our results revealed variability in the quality of hospitals included in the random effects model. In other words, this means that, adjusting for other factors, subsequent 30-day readmission is still more represented in some hospitals than others in Portugal. Several facts linked to the geographic inequities in the Portuguese health care system can explain this finding. First, there are remarkable inequities in the allocation of medical human resources and materials in Portugal (41, 42). For example, doctors and human resources are concentrated in Lisbon and Porto, with a lack in the number of doctors in the remote areas (23, 43). Second, patients' socioeconomic characteristics can contribute to this difference in readmissions between hospitals. It is well-known that socioeconomic characteristics are important indicators for health inequalities in Portugal (40, 44). However, some districts in Portugal, namely, the coastal regions, show higher concentrations of younger populations, higher levels of socio-economic indicators, better rates of economic growth, and, as a result, better health status and outcomes (23). In contrast, areas with lower socioeconomic status show poor geographical accessibility (44), and this variation in geographical accessibility affect utilization of health services (45). These findings demand interventions that guarantee health equity and require further analysis of any possible variations in hospital's practices by region that can be associated with higher rates of 30-day readmission.

In addition, our findings revealed that the seven hospitals presenting lower quality are large-scale hospitals that receive large numbers of admissions and with higher bed capacity in comparison to hospitals presenting higher quality. Moreover, the same hospitals have CMI classified by C, D, E, or F, meaning they receive patients in worse conditions when

compared to the rest of hospitals included in our study, while hospitals with better quality (less 30-day readmissions) present a lower CMI, meaning they receive patients in a less complicated condition: B, C, or D. These findings warrant further discussions, such as how the CMI can affect the subsequent 30-day readmission.

This study was based on the Portuguese national data for hospital admissions, from which HIV patients were analyzed. Its main strength is providing information on rates and indicators of hospitalizations among HIV patients with subsequent 30-day readmission among all registered admissions in Portugal, resulting in data, which could be used to develop a national health policy to avoid unnecessary readmissions. The aim of this study is in line with the Portuguese national policy of cost reduction and with the recommendations of both the World Health Organization and the European Observatory on Health Systems and Policies which emphasize that “the pursuit of efficiency is one of the central preoccupations of health policymakers and managers, and it is justifiably a cause for such concern” (34). Therefore, reducing hospital readmission rates should be a national priority and health policies should be examined and customized, considering the determinants of readmissions. The main limitation of this study is lacking additional socio-economic factors such as education, income, marital status, and clinical factors to better characterize disease status such as CD4 cell count, HIV RNA <400 copies/ml, and ART at discharge, which are not included in the data collected, and could serve as important indicators for premature readmission. Moreover, number of 30-day readmissions could be underestimated due to death occurring after discharge but within the 30-day period. The subsequent readmission rate of 13.2 in our results assists as a base of comparison for evaluating the quality of inpatient admissions among HIV patients in Portugal. This study offers a unique glimpse for health professionals and policymakers to focus readmission prevention strategies toward patients who are at high risk of readmission including males, elderly, patients who exit AMA, and patients with multiple comorbidities. In particular, it is important to adopt approaches that can address the factors associated with high-risk of readmission and to determine how to decrease any possibly unnecessary readmissions among HIV patients in Portugal.

CONCLUSION

We should bear in mind that the shift of HIV infection from a fatal disease into a chronic illness carries substantial challenges to the health system, in terms of hospitalization, readmissions, and the costs associated in the light of limited resources. Findings from our study, supported by a large database to examine 30-day readmission, can help to develop a national health policy to avoid unnecessary readmissions. These findings can set the basis for new insights that can focus on readmission prevention strategies toward patients who are at high risk of readmission, as explained in our study. Moreover, since the study was able to determine differences in hospital quality, this can set the basis for

an action plan that can target hospitals with less quality and to further investigate the reason behind lower quality.

DATA AVAILABILITY STATEMENT

The datasets analyzed in this article are not publicly available. Requests to access the datasets should be directed to <http://www.acss.min-saude.pt/>.

ETHICS STATEMENT

This study was approved by the Ethics Committee of the Institute of Hygiene and Tropical Medicine (IHMT), Lisbon. This is a secondary analysis of data routinely collected in Portuguese public hospitals, which was conducted under the supervision of the Central Administration of the Health System (ACSS), the legal owner of the DRG database in Portugal. The Ethics Committee of the Institute of Hygiene and Tropical Medicine (IHMT), Lisbon waived the requirement for written informed consent for participants in this study due to the anonymous and confidential nature of the data obtained from the ACSS in which the authors cannot identify any subject on that database, in accordance with the national legislation, the institutional requirements and the Portuguese National Authority of Data Protection for the creation of an individual database.

AUTHOR CONTRIBUTIONS

AS performed the formal statistical analysis, interpreted the data, drafted and revised the manuscript. SD, ZM, and BP helped in the interpretation of the data and reviewed the manuscript. SD helped in performing the statistical analysis. MM supervised and helped in performing the statistical analysis, supervised the interpretation of data, reviewed the manuscript, and managed and coordinated responsibility for the research activity planning and execution. AS and MM defined the study hypotheses, conceptualization, and designed the investigation. All authors contributed to the discussion of the result, reviewed the submitted manuscript and approved the manuscript for submission.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Paper IV

RESEARCH ARTICLE

Open Access

Statistical models for analyzing count data: predictors of length of stay among HIV patients in Portugal using a multilevel model



Ahmed Nabil Shaaban^{1,2*} , Bárbara Peleteiro^{2,3} and Maria Rosario O. Martins¹

Abstract

Background: This study offers a comprehensive approach to precisely analyze the complexly distributed length of stay among HIV admissions in Portugal.

Objective: To provide an illustration of statistical techniques for analysing count data using longitudinal predictors of length of stay among HIV hospitalizations in Portugal.

Method: Registered discharges in the Portuguese National Health Service (NHS) facilities Between January 2009 and December 2017, a total of 26,505 classified under Major Diagnostic Category (MDC) created for patients with HIV infection, with HIV/AIDS as a main or secondary cause of admission, were used to predict length of stay among HIV hospitalizations in Portugal. Several strategies were applied to select the best count fit model that includes the Poisson regression model, zero-inflated Poisson, the negative binomial regression model, and zero-inflated negative binomial regression model. A random hospital effects term has been incorporated into the negative binomial model to examine the dependence between observations within the same hospital. A multivariable analysis has been performed to assess the effect of covariates on length of stay.

Results: The median length of stay in our study was 11 days (interquartile range: 6–22). Statistical comparisons among the count models revealed that the random-effects negative binomial models provided the best fit with observed data. Admissions among males or admissions associated with TB infection, pneumocystis, cytomegalovirus, candidiasis, toxoplasmosis, or mycobacterium disease exhibit a highly significant increase in length of stay. Perfect trends were observed in which a higher number of diagnoses or procedures lead to significantly higher length of stay. The random-effects term included in our model and refers to unexplained factors specific to each hospital revealed obvious differences in quality among the hospitals included in our study.

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Conclusions: This study provides a comprehensive approach to address unique problems associated with the prediction of length of stay among HIV patients in Portugal.

Keywords: Length of stay (LOS), Count data analysis, HIV, Hospital performance, Quality indicator, Random - effects model, Multilevel model#

Background and introduction

Length of stay (LOS) is a key instrument to assess the quality of care in light of recent attempts to control the increasing costs of health care services [1–3]. The number of days a patient stays at the hospital represents a good illustration of resources utilized during the in-patient hospitalization [4]. Shorter inpatient stays reduce hospital resources consumption; hence, decrease the related health expenditure [5]. However, although hospitals are acclimating to clinical and financial standards induced by policy reforms to reduce length of in-patient care, hospitals' quality tends to vary widely [4]. In our previous paper [3], we shed light on the importance of length of stay as a quality indicator in Portugal. Determining the factors that may push LOS further may add to efforts in controlling unnecessary days of admissions, planning resources allocation, and customizing appropriate interventions [4, 5]. Unfortunately, the use of common statistical techniques, particularly the ordinary least squares (OLS) and the logistic regression, to analyze the predictors of LOS as a count variable with overdispersion can violate the assumptions behind each technique, leading to biased estimates that do not precisely reflect the observed data [3, 6, 7] (for an informative overview of count distribution see Atkins, Baldwin, Zheng, Gallop, & Neighbors, 2013 [8]). Relatively recently, several statistical models have been generated to analyze data with count nature [3, 9, 10].

The first model to analyze count outcomes is the Poisson regression model (PRM) [6, 11, 12]. This model is based on Poisson distribution has two restrictive assumptions [6, 12, 13]. First, the variance of the count outcome is equal to the mean. The second assumption is that occurrences of events are independent of each other [6, 12]. However, in practice, these assumptions are usually violated [6, 12], and count variables tend to have a conditional variance that often exceeds the conditional mean, which is known as "overdispersion" [6, 14]. Using the PRM to analyze outcomes in which one of these two assumptions is violated may result in biased data with underestimated standard error [12].

The second model is the negative binomial regression model (NBRM) that attempted to overcome the above-mentioned limitations in the Poisson distribution and has proven to properly represent the observed counts than the Poisson distribution [6, 15]. Accordingly, unlike

the PRM, this distribution does not require the mean and variance of the count outcome to be equal [6, 12]. Additionally, the previously mentioned assumption of independence of events required for PRM is no longer mandatory in the NBRM since it assumes that events can be repeated, given the influence of individual differences on the probability of an event to occur [6, 12, 13].

Two other alternatives count models are the Zero-Inflated Count Models: zero-inflated Poisson (ZIP) and zero-inflated negative binomial (ZINB). These models had been developed to overcome circumstances in which the origin of overdispersion is due to excessive zero counts. These kinds of distributions assume that the zero counts originate from two different sources and can be classified into two groups [16]. The first group is the "structured zeros" in which there is no chance to go beyond zero [16, 17]. For example, some HIV patients may have been admitted to a hospital and discharged on the same day (same-day separation) because they do not need further treatment, and hence, counted as a zero-length of stay (in days). This phenomenon of same-day separation can be explained by the fact that advancements in healthcare services, medical treatment, and technologies have allowed health facilities to provide more efficient services and improve patients' outcomes [18]. As a result, a steady decrease in length of stay and an increase in the probability of same-day separations can be observed [18]. These hospitalizations with same-day separations ($LOS = 0$) which partially constitute the zero counts should be distinguished from the overnight stays ($LOS = 1$) for resource allocation purposes. On the other hand, the remaining patients with zero count are classified as the "sampling or random zero" group [16, 17] as they can be admitted for more than zero days, e.g. a patient who could have been hospitalized for a non-zero number of days but decides to exit against medical advice before completing overnight stay and hence counted as zero number of days. The first two count models, Poisson and negative binomial are not sufficiently fit for this kind of data since they may fail to address the excess zeros that arise from two different data generating methods, and hence, may induce overestimated variance of model parameters [5]. After considering the excessive zero problem, the zero-inflated techniques generate two regression models. The first model predicts the occurrence of the count, while the

second regression model predicts the frequency of occurrence of this count [6, 11]. The zero-inflated model selection, whether ZIP or ZINB, is determined by the sort of overdispersion. If the excessive number of zeros generates the overdispersion, then the ZIP is more appropriate to model count data [6, 11]. On the other hand, if the overdispersion is caused by factors not related to the excessive number of zeros, then the ZINB model is more suitable [6, 11].

However, in some specific contexts in which hierarchically structured data are the norm, as in the case of a patient in hospital multilevel data, the use of the above-mentioned ordinary count models may violate the assumption of independence of variance of the ordinary count regression [5, 19]. The multilevel models (or the random-effects models) are becoming increasingly popular in the social, behavioral, and medical sciences in which hierarchically structured data [20, 21]. In Diagnosis Related Group (DRG) data, as in our study, patients tend to cluster within hospitals based on their preferences such as neighborhood, trust in a specific physician, or hospital, and hence violating the assumption of independence of variance of the ordinary count regression [5, 19]. Accordingly, multilevel modelling is more appropriate than ordinal count regression when dealing with data arranged in a hierarchical structure, such as patients nested within hospital two-level data [22–24]. Random-effects models can help in identifying outstanding hospitals and assess hospital quality accordingly [18]. Additionally, ignoring the existence of within-hospital clustering, as in-patient level analysis with no hospital random effect terms generates serious technical problems [20]. Disregarding this clustering will lead to an increase in the number of independent observations at the hospital level, thus underestimating the standard errors of regression coefficients at the hospital's level [20, 25, 26]. Therefore, the random-effects model is more relevant to analyze the impact of a set of predictors on LOS while controlling for variations in hospitalizations and hospital characteristics [25–27].

In Portugal, hospitalizations among HIV/AIDS patients account for the highest average LOS and represent a substantial economic burden, being classified as the second major diagnosis category [3, 28]. Moreover, it is important to understand whether the zero-inflated data can affect selecting the appropriate count regression model. Previous studies among HIV hospitalizations in Portugal either used logistic regression [28] or Poisson regression [29] to analyze a count variable with overdispersion. Accordingly, unlike other studies, this study aims to examine the predictors of LOS using the best count fit model through comprehensive comparisons between the different count models using the national admissions database among HIV patients in Portugal.

Methods

Data collection and source

The present analysis is based on data collected as part of the national registry of discharges among the Portuguese National Health Service (NHS) facilities. We reviewed hospitalization records for all HIV/AIDS patients admitted in Portugal between 1st January, 2009, and 31st December, 2017. Each record corresponds to a discharge episode and contains information collected while the patients were admitted to the hospital, such as type of admission, principal diagnosis, secondary diagnoses, procedures, region, age, sex, and discharge status. These data are anonymous, refers to the Diagnosis Related Groups (DRGs), and were obtained through the Central Health System Administration (ACSS) [30]. The DRGs were first introduced in Portugal through a pilot study in 1984, and since 1989 a systematic collection of DRGs applies to NHS hospitals [19, 31, 32]. Implementing DRGs in Portugal aimed to increase transparency and vindicate the allocation of resources to NHS hospitals by connecting inpatient care resources to hospital outcomes [31]. Since August 2006, there is only one non-modified version of DRGs in use in Portugal, known as All Patients DRGs version 21 (AP-DRGs version 21) [32]. This version is implemented in all Portuguese NHS hospitals and applies to all inpatients and ambulatory surgery with an exception for patients treated in psychiatric and rehabilitation care settings [31]. The AP-DRGs version 21 includes 669 DRGs under 25 Major Diagnostic Categories (MDCs), and each MDC refers to one organ or physiological system, with the MDC 24 corresponding to HIV Infection [31]. Since 1984, diagnoses and procedures within the DRGs system have been coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and since 2016 they have been coded using ICD-10-CM [31, 33].

The collection and validation of the DRG database in Portugal are carried out through several internal and external auditing steps to ensure high-quality data, a criterion necessary for any DRG system [31]. Coding in Portugal is first standardised and performed by physicians with specific training in coding [31]. An internal auditor assigned by each hospital supervises the data collection and the coding process. Afterward, the external coding auditing process starts with trained physicians supervised by a senior manager from the ACSS to assist and monitor the internal auditing process [31]. Moreover, this external auditing team is authorized to carry out visits for the included hospitals and validate patients' records to ensure if the DRG coding and classification have been done correctly [31]. It is also important to mention that the DRG clinical coding process is carried out through computer software to identify data errors and discrepancies in hospital records [31]. Afterward,

this software delivers data regarding the mean number of codes per record, the proportion of incorrect codes and coding errors, together with notifying the operator of deficient information within the records such as duplications, undefined primary diagnosis, or atypical lengths of stay [31]. We also used a unique fictional code included in the data for data validation that allows determining how many episodes correspond to the same user in the same institution, hence avoid duplicates. This fictional code does not identify the user or allow its identification afterward.

Study participants

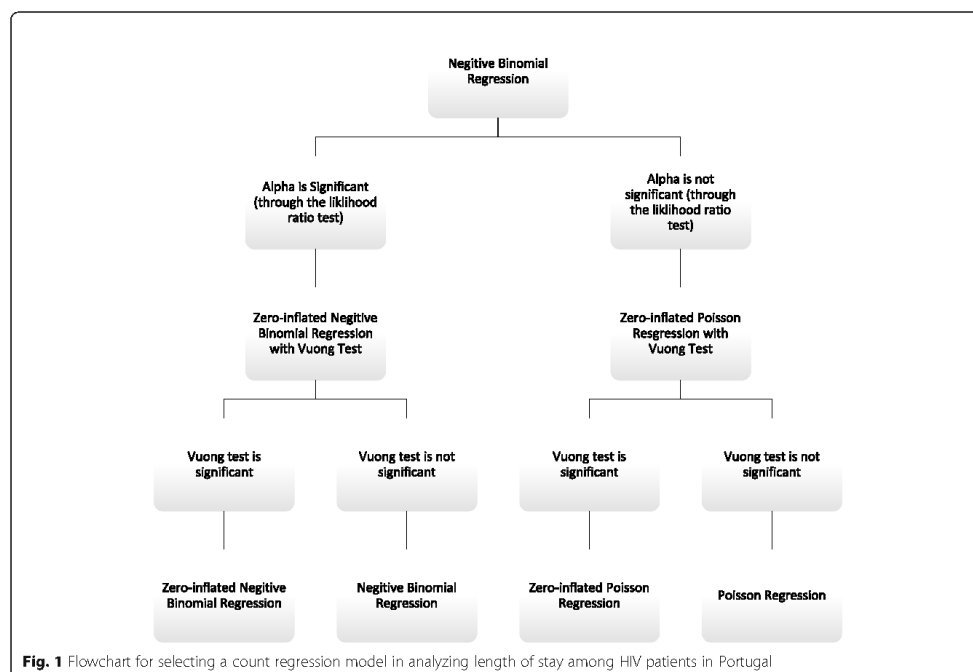
A total of 26,505 discharges among patients aged 18 years or older were included in the study. We considered only discharges classified under MDC created for patients with HIV infection (MDC 24). For the purpose of this study, data about discharges with HIV/AIDS as a main or secondary cause of admission were analyzed. Primary and secondary diagnoses and procedures were coded according to the International Classification of Diseases. Nineteen secondary diagnoses and up to 20 procedures were considered in this study.

Dependent variable

The dependent variable in our study is length of stay (LOS) which is defined as the number of days between in-patient admission and hospital discharge.

Data analysis

Descriptive and univariate analyses were carried out. A p -value ≤ 0.05 was considered to be significant. To select the best count model, we applied several strategies that included three separate phases. The first phase in our analysis was to test the overdispersion of our count variable. Accordingly, the mean and the variance of LOS were calculated. In the second phase of our analysis, we included a flowchart (Fig. 1) to assist in deciding the most fitting count technique. By using STATA® software, we confirmed overdispersion, this time by using the likelihood ratio test to examine for overdispersion. We took the advantage that STATA® automatically calculates the likelihood-ratio (LR) whenever a negative binomial model is applied to examine if the dispersion parameter is equal to zero [6] (for more informative overview of the LR see Long, 1997 [34]). The following stage in the second phase of our analysis included the evaluation of the excessive zero counts, which is represented by the left half of our flowchart. We used Vuong test to



examine any significant increase in the zero counts by considering the predicted probabilities of two count models [34].

In the third phase of our analysis, an exploratory analysis using the “countfit” estimation command in STATA* [35] was done to distinguish the corresponding fit of the different count models. Model performance and estimates of precision for each of the models were calculated. The command also generates the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), which are estimators of the corresponding quality of statistical models [36, 37]. Each test estimates the quality of each of the four models compared to each of the other models. Hence, they provide an approach for model selection. Accordingly, we examined the model fit by comparing the AIC, BIC, and predicted and observed probabilities of each count outcome for each probability distribution. To show the effect of choosing a model in which its assumptions are violated, the ordinary linear regression model was included in our study for the purpose of comparison.

In our multivariable analyses, to assess the effect of covariates on LOS, information on patients, clinical characteristics, admissions' characteristics were extracted from the hospital discharge database. The following potential determinants of LOS were considered: age (1 = “18–29”, 2 = “30–39”, 3 = “40–49”, 4 = “50–59”, 5 = “60–69”, 6 = “> 70”), gender (0 = male, 1 = female), region (0 = Non-resident, 1 = Norte, 2 = Centro, 3 = Lisbon, 4 = Alentejo, 5 = Algarve), HIV/AIDS as a primary diagnosis (0 = no, 1 = yes), having national health coverage (SNS) (0 = no, 1 = yes), admission status (0 = elective, 1 = emergency), treatment classification (0 = medical, 1 = surgical), number of diagnoses (0 = “<=5”, 1 = “6–8”, 2 = “9–12”, 3 = “> 12”), number of procedures (0 = “<=4”, 1 = “5–7”, 2 = “8–9”, 3 = “> 9”), in-hospital death (0 = no, 1 = yes), transferred admission (0 = no, 1 = yes), 30-day readmission (0 = no, 1 = yes), tuberculosis (TB) (0 = no, 1 = yes), Hepatitis B (0 = no, 1 = yes), Hepatitis C (0 = no, 1 = yes), Pneumocystis (0 = no, 1 = yes), Cytomegalovirus (0 = no, 1 = yes), Mycobacterial disease (0 = no, 1 = yes), Toxoplasmosis (0 = no, 1 = yes), Candidiasis (0 = no, 1 = yes), Kaposi's sarcoma (0 = no, 1 = yes), history of recurrent pneumonia (0 = no, 1 = yes), weight loss (0 = no, 1 = yes), asymptomatic HIV (0 = no, 1 = yes). Since several hospitals have been merged in one hospital during the period between 2009 and 2017, we created a dummy variable (Merge) to categorize hospitals according to the merging status (0 = not merged, 1 = merged) to be able to study the effect of merging on hospital quality. We created a dummy variable for the years of admission in which years before the financial crisis and bailout in Portugal were coded as 0 (2009, 2010, and 2011),

while years after the financial bailout were coded as 1 (2012, 2013, 2014, 2015, 2016 and 2017).

After choosing the most appropriate count technique, and in addition to the fixed patient and clinical related factors, we incorporated a random hospital effects term to the negative binomial model to examine the dependence between observations within the same hospital. Multiple comparisons of hospital effects were done by constructing 95% confidence intervals (CI) for random-effects.

All analyses were conducted with STATA*, version 13 (StataCorp LP, College Station, Texas, USA), and MLwiN*, version 3.04 (University of Bristol, Bristol, UK). MLwiN is a specialized software package for fitting multilevel models [38].

Results

Table 1 summarizes the main characteristics of the study population. The study population was mostly composed of males (71.3%), with a median age of 44 years (interquartile range (IQR): 38–53)), with more than half living in Lisbon (52.9%), and almost 3% not being registered in the national health system. Admissions during 2009 accounted for 14.6% of the total admissions representing the highest admission rate, while admissions during 2017 accounted for 6.5% of admissions representing the lowest admission rate. A descending trend in the frequency of admissions was observed through the years. Most of the hospital admissions were preceded by an emergency (83.3%), with 12.0% of them resulting in the death of the patient, 6.4% were discharged to another health facility, and 4.1% exit against medical advice. In 9.5% of the admissions, the patient had to be transferred to another hospital, and in 11%, the patient had been re-admitted within 30 days of the last discharge. Most episodes were classified as medical (94.2%). The median number of procedures per episode was 8 (IQR: 5–12), whereas the median number of diagnoses was 7 (IQR: 5–10). HIV was the primary diagnosis in 67.6% of the hospital admissions, while 6.6% of the patients had asymptomatic HIV infection at hospital admission. Hepatitis C was the most frequent co-infection (25.1%), followed by tuberculosis (7.3%), pneumocystosis (7.0%), mycobacterial infections (6.5%), Hepatitis B (4.3%), and cytomegalovirus (2.5%).

The median LOS in our study was 11 days (IQR: 6–22). Figure 2 shows our dependent variable as zero-inflated, positively skewed, and over-dispersed with a mean of 17.9 days and a standard deviation of 22.4 days, indicating an obvious difference between the mean and median LOS. Moreover, to confirm overdispersion, results from the likelihood ratio test were significant, (LR $\chi^2(1) = 0.79$, $P < 0.001$), indicating overdispersed data. Therefore, the NBRM is more appropriate to analyze

Table 1 Characteristics of the study sample (N = 26,505)

	N	%
Gender		
Male	19,011	71.73
Female	7494	28.27
Age		
18–29	1436	5.42
30–39	6801	25.66
40–49	9375	35.37
50–59	5205	19.64
60–69	2303	8.69
> =70	1385	5.23
Region of residence (NUTS II)		
Non Resident	357	1.35
Norte	6453	24.35
CENTRO	3806	14.36
LISBON	14,033	52.94
ALENTEJO	326	1.23
ALGARVE	1530	5.77
Having SNS *		
Yes	756	2.85
No	25,749	97.15
Year		
2009	3863	14.57
2010	3735	14.09
2011	3576	13.49
2012	3537	13.34
2013	3146	11.87
2014	2502	9.44
2015	2223	8.39
2016	2189	8.26
2017	1734	6.54
HIV as a primary diagnosis		
No	8586	32.39
Yes	17,919	67.61
Asymptomatic HIV		
No	24,758	93.41
Yes	1747	6.59
Hepatitis B		
No	25,357	95.67
Yes	1148	4.33
Hepatitis C		
No	19,843	74.87
Yes	6662	25.13
Associated TB infection		
No	24,581	92.74

Table 1 Characteristics of the study sample (N = 26,505) (Continued)

	N	%
Yes	1924	7.26
Pneumocystis		
No	24,654	93.02
Yes	1851	6.98
Cytomegalovirus		
No	25,853	97.54
Yes	652	2.46
Mycobacterium disease		
No	24,779	93.49
Yes	1726	6.51
Candidiasis		
No	22,206	83.78
Yes	4299	16.22
Toxoplasmosis		
No	25,267	95.33
Yes	1238	4.67
Kaposi Sarcoma		
No	25,556	96.42
Yes	949	3.58
Weight loss		
No	25,649	96.77
Yes	856	3.23
Number of procedures		
< =5	7525	28.39
6–8	6720	25.35
9–11	5576	21.04
> 11	6684	25.22
Number of diagnosis		
< =5	9114	34.39
6–7	5514	20.80
8–10	5761	21.74
> 10	6116	23.07
Emergency Admission		
No	4424	16.69
Yes	22,081	83.31
30-day Readmission		
No	23,549	88.85
Yes	2956	11.15
Hospital Death		
No	23,316	88.0
Yes	3192	12.0
Recurrent Pneumonia		
No	26,326	99.32
Yes	179	0.68

Table 1 Characteristics of the study sample ($N = 26,505$) (Continued)

	N	%
Mode of transfer		
No transfer	23,995	90.53
Transferred ^b	2510	9.47
Hospital Death		
No	23,316	88.0
Yes	3192	12.0
30-day Readmission		
No	23,549	88.85
Yes	2956	11.15

NUTS II Nomenclatura de Unidades Territoriais para Fins Estatísticos, nível II (Nomenclature of territorial units for statistics, 2 level); R.A. Região Autónoma (Autonomous Region)

^a National Health Insurance

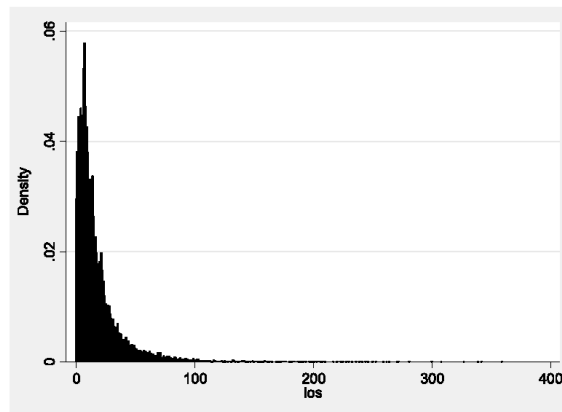
^b transfer for conducting exams or follow up or lack of resources or treatment of associated condition

LOS when compared to PRM. The second stage in the second phase of our analysis, which was dedicated to evaluating the excessive zero counts, shows that 784 participants were with zero values representing around 3.0% of the total admissions. Results from the Vuong test confirm the significant favorability of using the NBRM over the PRM ($z = 4.55$, $p < 0.001$).

Results from the “countfit” estimator in STATA show that NBRM and ZINB provide the best relative fit as they exhibited the least difference between the predicted and observed values and thus are preferred over the PRM and ZIP (Fig. 3). According to the figure, the best models are the models with estimates close to the zero line, the two negative binomial models. Being close to the zero line means that the predicted and the objected

values are close to each other. Under the same countfit command, results from the AIC and the BIC tests (Table 2) illustrate a notable reduction in the AIC and BIC measures of both the NBRM (198,008.241 and 198,352.015, respectively) model and ZINB model (197,424.156 and 198,103.519, respectively) which means better quality of models compared to the PRM (445,042.083 and 445,377.671, respectively) and ZIP (432,277.401 and 432,948.578, respectively). Accordingly, the NBRM and ZINB were the models of choice since they demonstrate the lowest difference between the predicted and observed estimates and the lowest AIC and BIC test results.

Table 3 presents the predictors of LOS according to the ordinary least square model, the four selected count

**Fig. 2** Length of stay distribution

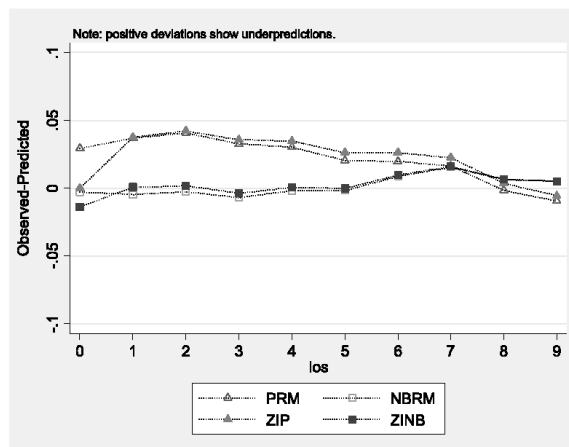


Fig. 3 Comparisons among observed versus predicted probabilities among count models ($N = 26,505$). PRM – Poisson Regression Model; NBRM – Negative Binomial Regression Model; ZIP – Zero-inflated Poisson; ZINB – Zero-inflated Negative Binomial

models, and the random-effects model. The OLS model results produced values that are overstating the actual coefficients compared to the count models. Regarding the negative binomial model with random-effects, admissions among males or admissions associated with TB infection, pneumocystis, cytomegalovirus, candidiasis, toxoplasmosis, or mycobacterium disease exhibit a highly significant increase in LOS. Moreover, perfect

trends were observed in which a higher number of diagnoses or procedures lead to significantly higher LOS. On the other hand, admissions associated with Hepatitis C, HIV as the primary diagnosis, asymptomatic HIV, recurrent pneumonia, or weight loss show a statistically significant LOS decrease. Lower LOS was also observed among admissions registered in Norte, Centro, or Lisbon regions. Moreover, similar findings were observed

Table 2 Tests and Fit Statistics (see the table in: Predicting length of stay from an electronic patient record system: a primary total knee replacement example)

PRM		BIC = 445,377.671	AIC = 445,042.083	Prefer	Over	Evidence
vs	NBRM	BIC = 198,352.015 AIC = 198,008.241 LR ^a	dif = 247,025.656 dif = 247,033.841 prob. = 0.000	NBRM NBRM NBRM	PRM PRM PRM	Very strong $p = 0.000$
vs	ZIP	BIC = 432,948.578 AIC = 432,277.401 Vuong ^b	dif = 12,429.093 dif = 12,764.682 prob. = 0.000	ZIP ZIP ZIP	PRM PRM PRM	Very strong $p = 0.000$
vs	ZINB	BIC = 198,103.519 AIC = 197,424.156	dif = 247,274.153 dif = 247,617.927	ZINB ZINB	PRM PRM	Very strong
NBRM		BIC = 198,352.015	AIC = 198,008.241	Prefer	Over	Evidence
vs	ZIP	BIC = 432,948.578 AIC = 432,277.401	dif = -2.346e+ 05 dif = -2.343e+ 05	NBRM NBRM	ZIP ZIP	Very strong
vs	ZINB	BIC = 198,103.519 AIC = 197,424.156 Vuong ^b	dif = 248.497 dif = 584.085 prob. = 0.000	ZINB ZINB ZINB	NBRM NBRM NBRM	Very strong $p = 0.000$
ZIP		BIC = 432,948.578	AIC = 432,277.401	Prefer	Over	Evidence
vs	ZINB	BIC = 198,103.519 AIC = 197,424.156 LR ^a	dif = 234,845.060 dif = 234,853.245 prob. = 0.000	ZINB ZINB ZINB	ZIP ZIP ZIP	Very strong $p = 0.000$

PRM Poisson Regression Model, NBRM Negative Binomial Regression Model, ZIP Zero-inflated Poisson, ZINB Zero-inflated Negative Binomial

^a Verified with a likelihood ratio test

^b Verified with the Vuong test

Table 3 Regressions on Length of Stay (*N* = 26,505)

	Linear Regression (OLS)	Negative Binomial Regression	Poisson Regression	Zero-inflated Poisson Regression	Zero-inflated Negative Binomial	Random-effects Model
Gender						
Male	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Female	-1.21*** (0.28)	-0.07*** (0.01)	-0.07*** (0.00)	-0.07*** (0.00)	-0.08*** (0.01)	-0.07*** (0.01)
Age						
18-29	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
30-39	0.06 (0.58)	0.00 (0.03)	-0.00 (0.01)	0.00 (0.01)	0.01 (0.03)	-0.02 (0.03)
40-49	0.66 (0.57)	0.05* (0.02)	0.03*** (0.01)	0.03*** (0.01)	0.05** (0.02)	0.02 (0.03)
50-59	-0.01 (0.60)	0.01 (0.03)	-0.00 (0.01)	-0.00 (0.01)	0.01 (0.03)	-0.00 (0.03)
60-69	-1.07 (0.68)	-0.03 (0.03)	-0.07*** (0.01)	-0.07*** (0.01)	-0.03 (0.03)	-0.04 (0.04)
> 70	-1.64* (0.76)	-0.06* (0.03)	-0.09*** (0.01)	-0.08*** (0.01)	-0.05* (0.03)	-0.07* (0.04)
Region of residence (NUTS II)						
Non resident	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Norte	-5.55*** (1.09)	-0.35*** (0.05)	-0.30*** (0.01)	-0.30*** (0.01)	-0.35*** (0.05)	-0.34*** (0.07)
Centro	-1.68 (1.12)	-0.13*** (0.05)	-0.09*** (0.01)	-0.11*** (0.01)	-0.14*** (0.05)	-0.28*** (0.07)
Lisbon	-2.50* (1.07)	-0.17*** (0.05)	-0.13*** (0.01)	-0.13*** (0.01)	-0.18*** (0.05)	-0.20*** (0.06)
Alentejo	-0.16 (1.53)	-0.09 (0.07)	0.00 (0.02)	0.01 (0.02)	-0.10 (0.07)	-0.15 (0.11)
Algarve	3.31** (1.19)	0.15*** (0.05)	0.20*** (0.01)	0.19*** (0.01)	0.14*** (0.05)	-0.06 (0.11)
Years after economic crisis						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	-1.63*** (0.27)	-0.07*** (0.01)	-0.09*** (0.00)	-0.09*** (0.00)	-0.07*** (0.01)	-0.06*** (0.01)
Having SNS^a						
Yes	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
No	-0.20 (0.74)	0.02 (0.03)	-0.00 (0.01)	-0.01 (0.01)	0.01 (0.03)	0.03 (0.04)
HIV as a primary diagnosis						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	-0.44 (0.30)	-0.05*** (0.01)	-0.04*** (0.00)	-0.04*** (0.00)	-0.05*** (0.01)	-0.04** (0.02)
Asymptomatic HIV						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	-3.88*** (0.54)	-0.28*** (0.02)	-0.28*** (0.01)	-0.25*** (0.01)	-0.27*** (0.02)	-0.27*** (0.03)
Hepatitis B						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	0.19 (0.61)	0.01 (0.03)	-0.00 (0.01)	0.00 (0.01)	0.01 (0.03)	0.03 (0.03)
Hepatitis C						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	-2.74*** (0.30)	-0.16*** (0.01)	-0.16*** (0.00)	-0.15*** (0.00)	-0.16*** (0.01)	-0.15*** (0.02)
Associated TB infection						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	9.40*** (0.48)	0.50*** (0.02)	0.43*** (0.00)	0.43*** (0.00)	0.50*** (0.02)	0.52*** (0.02)
Pneumocystis						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	1.28* (0.50)	0.11*** (0.02)	0.06*** (0.01)	0.06*** (0.01)	0.10*** (0.02)	0.08*** (0.03)
Cytomegalovirus						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	10.96*** (0.80)	0.34*** (0.03)	0.32*** (0.01)	0.32*** (0.01)	0.34*** (0.03)	0.31*** (0.04)
Mycobacterium disease						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)

Table 3 Regressions on Length of Stay (*N* = 26,505) (Continued)

	Linear Regression (OLS)	Negative Binomial Regression	Poisson Regression	Zero-inflated Poisson Regression	Zero-inflated Negative Binomial	Random-effects Model
Yes	2.21*** (0.50)	0.09*** (0.02)	0.10*** (0.01)	0.10*** (0.01)	0.09*** (0.02)	0.07*** (0.03)
Candidiasis						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	4.81*** (0.35)	0.22*** (0.01)	0.20*** (0.00)	0.20*** (0.00)	0.22*** (0.01)	0.19*** (0.02)
Toxoplasmosis						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	10.31*** (0.58)	0.46*** (0.02)	0.40*** (0.01)	0.39*** (0.01)	0.46*** (0.02)	0.45*** (0.03)
Kaposi Sarcoma						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	0.31 (0.66)	-0.01 (0.03)	0.00 (0.01)	0.01 (0.01)	-0.01 (0.03)	-0.02 (0.03)
Recurrent Pneumonia						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	7.90*** (1.49)	-0.44*** (0.07)	-0.46*** (0.02)	-0.47*** (0.02)	-0.44*** (0.07)	-0.46*** (0.08)
Weight loss						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	-3.21*** (0.70)	-0.15*** (0.03)	-0.15*** (0.01)	-0.15*** (0.01)	-0.15*** (0.03)	-0.12*** (0.04)
Number of diagnosis						
< -5	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
6 7	2.54*** (0.35)	0.19*** (0.02)	0.19*** (0.00)	0.17*** (0.00)	0.18*** (0.02)	0.19*** (0.02)
8 10	5.17 (0.36)	0.35*** (0.02)	0.34*** (0.00)	0.32*** (0.00)	0.34*** (0.02)	0.36*** (0.02)
> 10	10.47 (0.40)	0.55*** (0.02)	0.56*** (0.00)	0.54*** (0.00)	0.54*** (0.02)	0.55*** (0.02)
Number of procedures						
< -5	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
6 8	2.54*** (0.34)	0.27*** (0.01)	0.25*** (0.00)	0.21*** (0.00)	0.25*** (0.01)	0.34*** (0.02)
9 11	5.36*** (0.37)	0.45*** (0.02)	0.44*** (0.01)	0.39*** (0.01)	0.44*** (0.02)	0.54*** (0.02)
> 11	14.37*** (0.39)	0.82*** (0.02)	0.79*** (0.00)	0.74*** (0.00)	0.80*** (0.02)	0.94*** (0.02)
Emergency Admission						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	-0.76* (0.34)	-0.01 (0.01)	-0.05*** (0.00)	-0.06*** (0.00)	-0.02 (0.01)	0.02 (0.02)
30-day Readmission						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Yes	-1.41*** (0.39)	-0.03** (0.02)	-0.07*** (0.00)	-0.06*** (0.00)	-0.03* (0.02)	-0.01 (0.02)
Type of intervention						
Medical	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Surgical	9.67*** (0.54)	0.34*** (0.02)	0.41*** (0.01)	0.41*** (0.01)	0.36*** (0.02)	0.32*** (0.03)
Mode of transfer						
No transfer	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Transferred ^b	-6.63*** (0.57)	-0.32*** (0.02)	-0.35*** (0.01)	-0.33*** (0.01)	-0.32*** (0.02)	-0.35*** (0.04)
Destination after discharge						
Home	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Another health service ^c	6.31*** (0.68)	0.20*** (0.03)	0.30*** (0.01)	0.34*** (0.01)	0.21*** (0.03)	0.22*** (0.04)
Exit against medical advice	-4.73*** (0.63)	-0.44*** (0.03)	-0.42*** (0.01)	-0.35*** (0.01)	-0.43*** (0.03)	-0.43*** (0.03)
In hospital death	-0.70 (0.39)	-0.07*** (0.02)	-0.05*** (0.00)	0.01** (0.00)	-0.06*** (0.02)	-0.11*** (0.02)
Merged hospitals						
No	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)

Table 3 Regressions on Length of Stay ($N = 26,505$) (Continued)

	Linear Regression (OLS)	Negative Binomial Regression	Poisson Regression	Zero-inflated Poisson Regression	Zero-inflated Negative Binomial	Random-effects Model
Yes	-3.29*** (0.31)	-0.19*** (0.01)	-0.17*** (0.00)	-0.17*** (0.00)	-0.19*** (0.01)	-0.09 (0.09)
Constant	13.33 (1.37)	2.43*** (0.06)	2.47*** (0.02)	2.54*** (0.02)	2.46*** (0.06)	2.38*** (0.09)
Observations	26,505	26,505	26,505	26,505	26,505	26,505
Number of groups						54

Standard errors in parentheses

NUTS II Nomenclatura de Unidades Territoriais para Fins Estatísticos, nível II (Nomenclature of territorial units for statistics, 2 level); R.A. Região Autónoma (Autonomous Region)

*** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$ ^a National Health Insurance^b transfer for conducting exams or follow up or lack of resources or treatment of associated condition^c special service includes Home service, Specialized aftercare, Palliative care, long-term hospital care

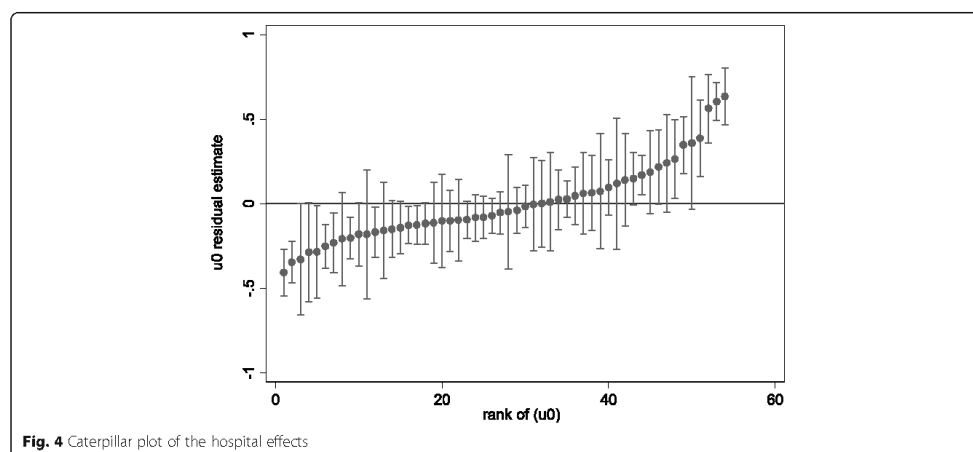
among hospitalizations associated with exited against medical advice, a transfer to another hospital, inpatient mortality, or hospitalizations that occurred in the years that followed signing the financial bailout program (after 2011). As expected, the standard error in the ordinary count models was underestimated when compared to the random-effects count regression model.

Fig. 4 represents the caterpillar plot of the hospital effects. The plot illustrates the random-effects model for 54 hospitals included in our study that was used to determine unmeasured and unobserved factors specific to each hospital with their respective 95% CI. The first nine hospitals have random-effects and respective 95% CI below zero, being considered with more quality when compared to the mean, whereas the last seven hospitals' random-effects exhibit higher LOS (random-effects and corresponding 95%CI above zero). The plot shows that the remaining hospitals, almost 70% of the hospitals included, cannot be distinguished from the overall average.

Discussion

This paper provides an illustration of statistical techniques that are appropriate to overcome obstacles linked to the prediction of count data with overdispersion using longitudinal predictors of LOS among HIV hospitalizations in Portugal. The advantages of the selected count models were presented and explained. To the best of our knowledge, this is the first study to consider analyzing LOS among HIV patients in Portugal by using the best count fit model after comparing the four aforementioned models.

The fact that applying different statistical techniques results in different results demonstrates the importance of precisely selecting a model that accurately represents the observed count data. In other words, we can say that this paper illustrates the consequences of using methods that do not precisely consider the nature of the data distribution. Analyzing LOS among HIV patients as a count variable with overdispersion will yield more precise

**Fig. 4** Caterpillar plot of the hospital effects

outcomes if the assumptions behind the selected model are not violated.

Previous studies in Portugal that analyzed LOS among HIV patients either used logistic regression [28] or Poisson regression [29] without explaining the theory and assumptions behind selecting the Poisson regression over the other count models. LOS as an overdispersed count variable is violating the assumption of using the Poisson model in which the variance of LOS should be equal to the mean. As shown in our results, linear regression through the OLS technique, whose assumptions were violated by the count distribution of LOS data, produced values that are overstating the actual coefficients compared to the count models. Moreover, the same linear model identified some factors (emergency admissions, merged hospitals, and 30-day readmission) as significantly decreasing LOS although they are not when compared to the most appropriate models, namely ZINB and the random-effects model. On the contrary, the linear model showed a non-significant decrease in LOS among admissions with HIV as a primary diagnosis, while the ZINB and random-effects model showed a significant decrease. In addition, and when compared to the zero-inflated negative binomial model or the random-effects model, the other count models underestimated the standard errors of regression coefficients. However, this result was expected, especially for the random-effects model, since accurate standard errors will be generated if variation at multilevel, patient, and hospital levels is allowed in the analysis [20, 25]. Ignoring the hierarchy in multilevel data will result in data that underestimate the magnitude of hospital level's standard errors of regression coefficients [20, 25]. The other technical problem is inflation in the number of independent observations at the hospital level of the hierarchy. For example, Poisson and ZIP identified some factors as significantly decreasing LOS, although they are not when compared to the random-effects model, namely 30-day readmission, merged hospitals, and emergency admissions. Moreover, all the included models showed a significant increase in LOS for admissions in Algarve, while the random-effects model, the most appropriate model, showed a non-significant decrease in LOS in the Algarve region. These findings can explain how using an inappropriate model may mislead policy making decisions.

The median LOS of 11 days in our study is equal to the median reported by a similar study in Brazil [39]. Shorter LOS was reported by similar studies in Spain (8 days) [40], United Kingdom (7.5 days) [41], and the United States (6 days) [42]. Moreover, the median of 11 days in Portugal is higher than the national Portuguese LOS average of 9 days [43]. On the contrary, higher LOS were reported in Colombia (14 days) [44], and Italy (16

days) [41]. Differences in LOS duration between countries can be explained by different applied policies on HIV infection control or different population samples among countries. This study pointed out several factors that tend to push LOS further after using the random-effects count model. First, socio-demographic factors indicate that admissions among females are frequently less prolonged than in men. This result is in accordance with a previous study in Ontario, Canada in which female sex was predictive of shorter hospital stays among HIV hospitalizations when compared to men [45]. This finding can be explained by the fact that male patients who are living with HIV carry a substantial burden of the disease with respect for severity [46], and morbidity [47], which can be reflected on LOS. Also, individuals who are registered as non-residents or individuals who are not registered in the National Portuguese Health System tend to have a significantly higher LOS. Since all Portuguese citizens and documented migrants are entitled to the NHS [48], this finding sheds light on how the migration status can affect health outcomes, especially among undocumented migrants in Portugal. Exit against medical advice was significantly associated with shorter hospital stays in our study. In general, exit against medical advice is associated with shorter stays and lower hospital charges at the beginning, as reported in previous studies [49, 50]. However, while this result is logical and expected, patients who exit against medical advice encounter a later higher risk of readmissions as shown in our previous study among HIV hospitalizations [26] or studies from other countries but among similar hospitalizations [51]. Accordingly, history of exit against medical advice can increase future utilization of healthcare resources [52]. Given this implication, further analysis of populations at risk and factors that can push exit against medical advice is mandatory to consider proper interventions.

Comorbidities were among the most important factors that tend to push LOS further. Also, comorbidities showed a perfect trend in which the higher number of comorbidities, diagnosis, or procedures were associated with higher LOS in days. Similar findings have been reported by a similar study in the United States in which the presence of comorbid conditions was a strong predictor of LOS [53]. The same study also defined the number of diagnoses and procedures as independent predictors of LOS [53]. Another study in Italy came to the conclusion that chronic diseases and comorbidities increase the costs of hospitalizations among HIV admissions [54]. Moreover, the presence of co-infections or AIDS-defining illnesses that are commonly associated with HIV patients led to a significant increase in LOS in our study. In general, these co-infections or AIDS-defining illnesses represent a major public health concern as they lead to patients' disabilities and adverse

hospital outcomes [44, 55–60]. These results from our study generally agree with those obtained in previous studies in other countries. For example, LOS was found to be significantly higher among individuals with HIV-TB coinfection in a study conducted in the United States [61]. Another study found that LOS and hospitalization costs were higher in the Hepatitis B-HIV co-infected patients compared to the Hepatitis B mono-infected patients or HIV mono-infected patients with statistically significant results [62]. Moreover, previous studies conducted in different countries defined Hepatitis C-HIV co-infection as a significant predictor of LOS and early readmissions among HIV admissions [40, 41, 63]. In addition, another study defined the presence of an AIDS-defining illness as independent predictors of LOS [53]. In our earlier work [26], comorbidities and coinfections were among the main factors to increase the probability of 30-day readmission among HIV patients in Portugal. Since comorbidities and coinfections tend to increase both inpatient LOS and 30-day readmission, further exploration of any flaws in outpatient care and continuity of care following discharge should be addressed. In other words, to ensure more efficient care, healthcare providers should guarantee the entire care continuum for improvements. By encouraging an overall patient care plan, providers can potentially improve health outcomes while at the same time reducing costs. Accordingly, it is in the hospitals' best interest to encourage communication, coordination, and follow-up with the primary care, rehabilitation centers, outpatient care, specialists, and general practitioners who are following their patients, even after they are discharged. In accordance with previous studies, HIV admissions associated with surgical interventions in our study were predictive of longer inpatient stays. These studies demonstrated that HIV/AIDS patients are more likely to develop surgical site infections and complications compared to the general population, hence, have longer LOS [64–66].

Years that followed the economic crisis in Portugal and culminated in signing the Economic Adjustment Program for Portugal, also known as the Bailout program, were associated with a significant decrease in LOS. Two facts can explain this phenomenon. First, by signing this Bailout program, Portugal was obligated to implement strict austerity measures that had led to a reduction of spending on sensitive health sectors, payments to NHS hospitals, day cases, and in-patients' admissions [3, 26, 67]. These measures have reduced hospital quality by reducing LOS and number of admissions or by substituting in-patient hospitalizations by day cases [3, 26, 67]. The second fact that can explain this phenomenon is the continuous reforms of the hospitals' sector in Portugal that translated into a 3 years

plan for hospitals reforming that have been monitored by the Regional Health Authority [26, 68]. These reforms that started in 2011 have positively affected quality levels, with a significant reduction in LOS [26, 68].

The random-effects term included in our model and refers to unexplained factors specific to each hospital revealed obvious differences in quality among the hospitals included in our study. In other words, LOS is still significantly higher in some hospitals than others in Portugal. The seven hospitals that showed significantly higher LOS requires further investigation. These hospitals' unexplained factors can range from discrepancies in medical expertise, health care, and human medical resources. However, this finding can be explained by how the health care system and the provided services can be affected by the socio-demographic inequalities in Portugal. These inequalities translate into an unfair distribution of medical resources, equipment, doctors, and nurses [69]. Moreover, some geographical areas in Portugal, particularly the coastal regions, exhibit higher concentrations of young populations and better economic growth indicators, leading to better health outcomes [69]. These findings necessitate a further examination of any potential discrepancies in the hospital's performance by region that can be associated with higher LOS.

This study used the entire Portuguese national data for public hospital admissions, from which HIV patients were analyzed. The main strengths of our study can be concluded in the following points. First, we used a large dataset representing the entire national Portuguese admissions in public hospitals. Second, our study provided a comprehensive review and comparison between statistical procedures for analyzing count data to select the most optimal model. Third, we used multilevel random effect predictions that can help in the identification of outstanding hospitals and may serve as an indicator to assess hospital quality/performance. Finally, the study provides information on indicators that can push LOS further, which can enlighten health policymakers to control unnecessary hospitalizations. The main limitation of our study is the absence of additional socio-economic factors, access to primary care indicators, and clinical factors such as immune status, CD4 cell count, and ART at discharge that may contribute to a better understanding of factors that can increase LOS. Moreover, LOS could be underestimated due to death occurring during admission and/or in-hospital stay. Findings from this study support the conclusion of the Portuguese Court of Auditors, stating that the techniques used to analyze LOS within the DRG system is insufficient and is not the most appropriate way [70]. Accordingly, using fairly recent statistical techniques presented in our study to address complexly distributed data, unique problems

associated with the prediction of LOS can be solved. Moreover, our study supports the Portuguese policy of cost reduction by preventing unnecessary spending [26]. Accordingly, LOS, as a quality/performance indicator, should be handled as a national priority, and health policies should be directed to consider addressing the determinants that can push it further.

Conclusion

Analyzing LOS among HIV patients will yield more precise results if the nature of LOS as a count outcome met the assumptions behind the used statistical method. Using suboptimal techniques can mislead health professionals and policymakers. Results from our study can help to target the factors that tend to increase length of stay among HIV patients in Portugal and hence reduce unnecessary spending, given the weight and the economic burden of HIV/AIDS hospitalizations.

Abbreviations

ACSS: Administração Central do Sistema de Saúde [Central Administration of the Health System]; AIC: Akaike information criterion; AIDS: Acquired Immunodeficiency syndrome; AP-DRGs version 21: All Patients Diagnosis Related Groups version 21; ART: Antiretroviral therapy; BIC: Bayesian information criterion; CI: Confidence intervals; DRG: Diagnosis Related Groups; HIV: Human immunodeficiency virus; ICD: International Classification of Diseases; IQR: Interquartile range; LOS: Length of stay; LR: likelihood-ratio; MDC: Major Diagnostic Category; NBRM: Negative binomial regression model; NHS: National Health Service (Portugal); OLS: Ordinary Least Squares; PLWHA: People living with HIV/AIDS; PRM: Poisson regression model; SNS: Serviço Nacional de Saúde [National Health Services Coverage]; TB: Tuberculosis; ZINB: Zero-inflated negative binomial; ZIP: Zero-inflated Poisson

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Authors' contributions

ANS performed the formal statistical analysis, interpreted the data, drafted and revised the manuscript. BP and MROM supervised and helped in performing the statistical analysis, supervised the interpretation of data, reviewed the manuscript, and managed and coordinated responsibility for the research activity planning and execution. ANS defined the study hypotheses, conceptualization, and designed the investigation. All authors contributed to the discussion of the result, reviewed the submitted manuscript, and approved the manuscript for submission.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

This is a secondary analysis of data routinely collected in Portuguese public hospitals in which the secondary use of personal data is regulated by a personal data protection legislation, and was conducted under the

supervision of the Central Administration of the Health System (ACSS) (<http://www.acss.min-saude.pt/>), Ministry of Health (Portugal), the legal owner of the DRG database in Portugal. The national legislations provide that, as a principle, health data must be anonymized for secondary use. Under Portuguese national laws and legislations, it is mandatory to inform the patient of the content of the electronic health records and their rights before the electronic health records are put in place. This article does not contain any studies with human participants performed by any of the authors. The data obtained from the ACSS is anonymous and confidential, in which the authors cannot identify any subject on that database, in accordance with the national legislation, the institutional requirements, and the Portuguese National Authority of Data Protection for the creation of an individual database.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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General discussion

This thesis provides valid estimates for hospital quality measures among HIV hospitalizations in Portuguese public hospitals. The work also aims to fill gaps in identifying factors that can affect these quality indicators. Claiming quality measures as a necessary way to limit health spending implies developing precise hospital benchmarks. It is thus important to collect data, and use quality and outcome measures to determine how well an entity is performing. Under such a hypothesis, comparable and comprehensive estimates of quality measures are mandatory to control health spending in general and disease-specific spending in particular, and are critical for evaluating health systems. Identifying significant factors that can affect these quality indicators can guide the process of reallocation of resources and efficiently use health resources. Additionally, increasing data on hospital quality measures contributes to a sustained decision-making process, enabling the evaluation of adopted measures and identifying intervention priorities.

In the present thesis, the economic burden of hospitalizations among HIV patients in Portugal and the role that quality indicators can play as a method of cost containment were reviewed (*Paper I*). The cost of HIV care in Portugal is a critical issue considering that there are approximately 42,000 PLWHA (408), with an average cost of € 14,000/patient per year (409). A simple calculation shows that the average annual cost of spending on HIV/AIDS in Portugal is €588 million per year. The progressive development in HIV/AIDS epidemiology and the course of the disease due to the introduction of ART has created challenges for the country's healthcare system. The longer lifespan of PLWHA, and the high infection incidence among vulnerable and most-at-risk populations have brought significant consequences to the healthcare system, especially as they associate with resources utilization and higher costs. It is important to know that this annual expenditure may not reflect the actual economic burden caused by HIV/AIDS as it does not comprise the indirect economic costs, such as productivity losses due to morbidity or mortality, which implies that the HIV/AIDS burden may far outweigh the considered costs. Moreover, *Paper I* pointed to the importance of investigating the determinants of 30-day readmission and LOS among HIV/AIDS patients in Portugal to assess factors that can further push these quality indicators. Predicting a specific disease's outcome is essential for planning and evaluating interventions and providing estimates for the utilized resource (410). Thirty-day readmissions and LOS provide perspectives to compare patient groups and assess the efficiency of interventions (410). A general procedure for

statistical analyses was proposed in *Paper I*, depending on the specific objectives of the proposed subprojects.

Paper II shows how the unexpected and unprecedented burden imposed by the COVID-19 pandemic in Portugal adds further support to the recommendations raised by *Paper I*. The pandemic has created an economic crisis alongside a healthcare crisis, as Portuguese hospitals and health system have stepped up to meet the unprecedented challenges. These measures include establishing testing centers, and creating isolation and intensive care units. Hospitals in particular carried a substantial burden due to several factors that include the effect of canceled and postponed medical appointments or services, and the generated unprecedented demand for medical supplies and equipment, such as ventilators and personal protective equipment, which have led to an increase in hospital expenditures. Given these devastating economic challenges in light of the COVID-19 pandemic, *Paper II* highlighted the urgent need to implement hospital quality indicators, namely 30-day readmission and LOS, in an attempt to mitigate the effect of the pandemic on the Portuguese health system. Considering the high financial burden of treating HIV/AIDS in Portugal, there is obvious potential in achieving this goal by controlling unnecessary spending on HIV/AIDS in the country. HIV/AIDS is a major cause of resources consumption in Portugal being classified as the second major diagnostic category (411).

Paper II also stressed the concern that the health system in Portugal may become a target for cost containment as a result of any inevitable economic global recession due to the COVID-19 pandemic. Lessons learned from the financial crisis that hit Portugal in 2011 showed that the fiscal austerity measures adopted by the country during that time resulted in budget cuts, reduction of spending on sensitive health sectors, and restructuring of numerous public entities, including the National AIDS Program (411-413). In general, and during economic crises, the health sector becomes vulnerable and a target for budget cuts owing to its size and the high potential for improved performance (414). In *Paper II*, we proposed that the decrease of unnecessary spending represented by high rates of 30-day readmissions or prolonged stays in hospital may help avoid such drastic austerity measures. This recommendation was supported by estimates that predicted Portugal to be among the most affected by any possible financial crisis compared to other countries, such as Brazil, China, or the US, due to the high contribution of tourism to the Portuguese economy (415).

The results from *Papers III* and *IV* provide practical application and further analysis of the recommendations raised by *Papers I* and *II*. *Paper III* estimated the rate of 30-day hospital readmission and analyzed factors associated with subsequent 30-day readmission among HIV

patients in Portugal. Hospital readmission rate has been praised as a quality measure and a means to control healthcare cost expenditures (9). Previous reviews supported the evidence that there is great potential for decreasing costs by targeting deficiencies in quality, and accordingly, we can maximize the benefits given the available resources (416-418). Developing and applying readmission reduction programs, which penalize hospitals for excess readmissions, have helped decrease hospital readmission rates (419). Results from *Paper III* show that the 30-day hospital readmission rate is 13.2% (95% CI: 12.9–13.6%). The subsequent readmission rate of 13.2 in our paper assists as a base of comparison for evaluating the quality of inpatient admissions among HIV patients in Portugal. The mean of inpatient bed days due to 30-day readmission in our study was 9,735 days per year (Table 4). Given that the average daily cost for HIV/AIDS admission is around € 825 (420), the average yearly expenditure due to 30-day readmissions is estimated to be € 8,031,375.

Table 4. The cost of thirty-day readmissions among HIV/AIDS admissions in Portugal (2009-2014).

Year	Total number of inpatient bed days due 30-day readmission N (%)	Estimated cost (Euros)*
2009	11,036	9,104,700
2010	10,160	8,382,000
2011	9,778	8,066,850
2012	10,942	9,027,150
2013	9,809	8,092,425
2014	6,686	5,515,950
Total	58,411	48,189,075

AIDS: Acquired Immunodeficiency Syndrome; HIV: Human Immunodeficiency Virus.

*The mean daily cost per admission is €825 (420).

Moreover, several risk factors were the main independent predictors of 30-day readmissions, or in other words, tend to increase the likelihood of 30-day readmissions. Previous studies urged for a greater understanding of which patients are at greater risk of readmissions to target these particular populations (1, 14, 421). Previous studies also emphasized that any attempt to assess early readmissions should focus on a defined inpatient's disease or disorder rather than assessing the general inpatient population as it results in a significant improvement in quality of care (46, 47, 422, 423). In our study, hospitalizations that included discharge against medical advice, scheduled admissions and TB infection exhibited a higher odds of hospitalizations with subsequent 30-day readmission. In contrast, hospitalizations among females, that included a transfer to another facility and having a responsible financial institution showed a lower odds of hospitalizations with subsequent 30-

day readmission. Hospitalizations associated with a higher number of diagnoses, older ages, or hospitalizations during the economic crisis showed an increasing trend of 30-day readmission, whereas an opposite trend was observed for hospitalizations with a higher number of procedures. Another relevant finding of this work is the variability in the quality of hospitals included in the random-effects model. In other words, this means that adjusting for other factors; subsequent 30-day readmission is still more represented in some hospitals in Portugal than others. Nine hospitals included in this study have random-effects and respective 95% CI below 1, being considered to have a greater quality when compared to the mean, while the random-effects of seven hospitals exhibit a higher likelihood of readmissions (random-effects and corresponding 95% CI above 1). Hospitals with less quality (more 30-day readmissions) have a CMI classified by C, D, E or F, meaning they receive patients in worse conditions when compared to the rest of the hospitals included in our study, while hospitals with better quality (less 30-day readmissions) present a lower CMI, meaning they receive patients in a less complicated condition: B, C or D. In addition, our findings revealed that the seven hospitals presenting lower quality are large-scale hospitals that receive large numbers of admissions and with higher bed capacity in comparison to hospitals presenting higher quality. These findings warrant further discussions, such as how the CMI and hospital characteristics can affect subsequent 30-day readmission.

Paper IV estimates the average LOS among HIV hospitalizations in Portugal and analyzes factors that can increase LOS, using the best fit methodological technique. LOS is an effective measure of inpatient quality of care and a significant determinant of the cost of healthcare provided (410). Accordingly, it is in the hospital's best interest to avoid unnecessary prolonged stays that consume considerable resources. In that context, assessing LOS or factors that can predict LOS enables developing effective customized strategies to reduce it (4). Results from *Paper IV* show the median LOS among HIV hospitalizations in Portuguese public hospitals to be 11 days (interquartile range: 6-22). This average is higher than the average of nine days recorded as LOS for all hospitalizations in Portugal (Figure 15) (64). The median LOS of 11 days in our study is equal to the median reported by a similar study in Brazil (424). Shorter LOS have been reported by similar studies in Spain (8 days) (425), United Kingdom (7.5 days) (426), and the US (6 days) (427). On the contrary, longer LOS have been reported in Colombia (14 days) (428) and Italy (16 days) (426). Differences in the duration of LOS between countries can be explained by different policies applied to HIV infection control or different population samples among countries.

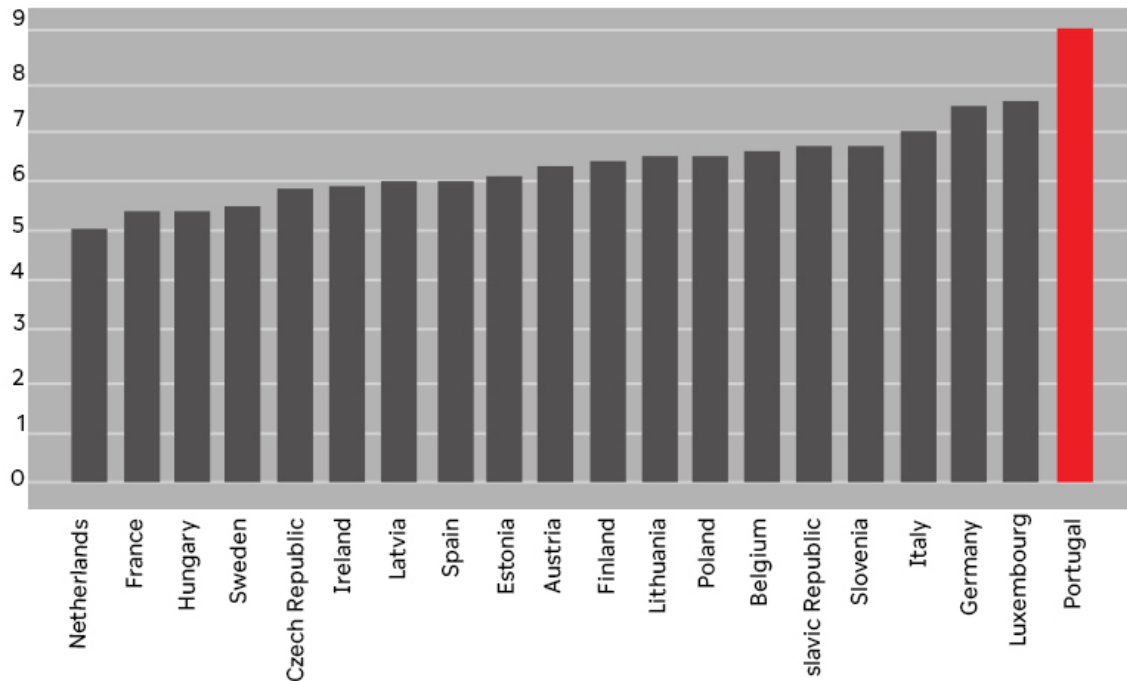


Figure 15. Length of hospital stay in the European Union.

Source: Organisation for Economic Co-operation and Development (OECD) (64).

The mean of inpatient bed days due to LOS above the 75 percentile (>22 days) in our study was 32,422 days per year (Table 5). Given that the mean daily cost per HIV admission is around € 825 (420), the average yearly expenditure due to LOS above the 75 percentile is estimated to be € 26,748,150. This average yearly expenditure can increase up to 36,529,350 for hospital stays above the median LOS (11 days).

Table 5. The cost of inpatients stays due to LOS above 22 days (2009-2017).

Year	Total number of inpatient bed days due to LOS above the 75 percentile	Estimated cost (Euros)*	Total number of inpatient bed days due to LOS above the 50 percentile	Estimated cost (Euros)*
2009	45,816	37,798,200	61,166	50,461,950
2010	41,387	34,144,275	56,817	46,874,025
2011	38,089	31,423,425	52,621	43,412,325
2012	36,119	29,798,175	49,947	41,206,275
2013	32,532	26,838,900	45,666	37,674,450
2014	28,695	23,673,375	38,635	31,873,875
2015	25,634	21,148,050	34,019	28,065,675
2016	24,292	20,040,900	33,439	27,587,175
2017	19,238	15,871,350	26,193	21,609,225

Total	291,802	240,736,650	398,503	328,764,975
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LOS: Length of Stay.

*The mean daily cost per admission is €825 (420).

Other findings from *Paper IV* support the views of considering the nature of LOS as an over-dispersed count variable as an important element in selecting the most suitable statistical technique, thus guaranteeing precise outcomes. Previous studies showed that the use of common statistical techniques, such as the ordinary least squares (OLS) or logistic regression, to analyze the predictors of a count variable with overdispersion can violate the assumptions behind each technique leading to biased estimates that do not precisely reflect the observed data (429). Previous studies in Portugal that analyzed LOS among HIV patients either used logistic regression (411) or *Poisson* regression (430) without explaining the theory and assumptions behind selecting *Poisson* regression over other count models.

Statistical comparisons across the count models included in *Paper IV* revealed that the random-effects negative binomial models provided the best fit with observed values. The linear regression model through the OLS technique, whose assumptions were violated by the count distribution of LOS data, produced values that are overestimating the actual coefficients in comparison with the count models. The linear model identified some factors (emergency admissions, merged hospitals and 30-day readmission) as significantly decreasing LOS although they are not when compared to the most appropriate models, namely the zero-inflated negative binomial model and the random-effects model. On the contrary, the linear model showed a non-significant decrease in LOS among admissions with HIV as a primary diagnosis, while the ZINB and random-effects model showed a significant decrease. Additionally, and when compared to the zero-inflated negative binomial model or the random-effects model, the other count models underestimated the standard errors of regression coefficients. Moreover, *Paper IV* showed that any study design that ignores the hierarchy represented by the multilevel nature of data will result in an increase in the number of independent observations at the hospital level, and thus, underestimating the standard errors of regression coefficients at the hospital level (431-433).

Paper IV pointed out several factors that tend to lengthen LOS after using the random-effects count model. Several risk factors were the main independent predictors of LOS. Admissions among males, those associated with discharge to another health service or admissions associated with surgical interventions exhibit a high significant increase in LOS. On the contrary, discharge against medical advice or admissions during the years that followed the economic crisis in Portugal and culminated in signing the Economic Adjustment Program

for Portugal, also known as the bailout program, were associated with a significant decrease in LOS. Moreover, perfect trends were observed in which a higher number of diagnoses or procedures led to significantly higher LOS. Comorbidities were among the most important factors that tend to lengthen LOS. Also, comorbidities showed a perfect trend in which a higher number of comorbidities, diagnoses or procedures were associated with a longer LOS in days. Additionally, the presence of co-infections commonly associated with HIV patients resulted in a marked significant increase in LOS, namely TB infection, pneumocystis, cytomegalovirus, candidiasis, toxoplasmosis or mycobacterium disease. These co-infections are well known to cause severe opportunistic infections in HIV patients, and thus, represent a major public health concern as they lead to patient disabilities (188, 428, 434-436).

The random-effects term included in *Paper IV*, which refers to unexplained factors specific to each hospital revealed obvious differences in quality among the hospitals included in our study. In other words, LOS is still significantly higher in some hospitals than others in Portugal. Seven hospitals that showed significantly longer LOS require further investigation. These unexplained factors of hospitals can range from discrepancies in medical expertise, healthcare and human medical resources. However, this finding can be explained by how the healthcare system and the services provided can be affected by sociodemographic inequalities in Portugal. These inequalities translate into an unfair distribution of medical resources, equipment, doctors and nurses. Moreover, some geographical areas, particularly the coastal line, exhibit higher concentrations of young populations, and economic growth, that result in better health outcomes. These findings require a further examination of any potential discrepancies in the performance of hospitals by region that can be associated with longer LOS.

Since results from *Papers III* and *IV* revealed comorbidities and coinfections as the main factors to increase both 30-day readmission and LOS, we recommend a further exploration of any flaws in outpatient care and continuity of care following discharge. To ensure more efficient care, healthcare providers should guarantee the entire care continuum for improvements. By encouraging an overall patient care plan, providers can potentially improve health outcomes while at the same time reducing costs. Accordingly, it is in the hospitals' best interest to encourage communication, coordination and follow-up with primary care, rehabilitation centers, outpatient care, specialists and general practitioners who are following patients, even after they are discharged. Evidence also supports the importance of involving clinical experts in interventions that aim to manage the care provided to patients with chronic disorders as it yields better patient and quality outcomes (1, 45-47, 422, 423, 437, 438). Other effective interventions to control chronic disorders, and hence, healthcare expenditures, include

health education, post-discharge follow-up, home monitoring and adherence to medications (1, 439). Moreover, previous studies have shown that many hospitalizations could be prevented with efficient management of chronic diseases in community-based or home care services (4). On the other hand, the lack of coordination with community health services leads to poor quality outcomes (440, 441). In that regard, many countries have developed the capacity of these settings to manage cases that are well enough to be discharged (4). For example, expanding the accessibility for intermediate care facilities has improved hospital transitions in several Nordic countries, the Netherlands and Scotland (4). Hospitals in these countries contact municipalities within 24 hours of patient admission if they assume the patient will need follow-up from an intermediate care facility or community care setting after being discharged to ensure better patient and hospital outcomes (4). Moreover, increasing the capacity of home-based services following discharge has resulted in decreasing LOS and early readmission (442). Furthermore, health policies aimed at rewarding better integrating primary care following hospital discharge through P4P and pay for coordination reimbursement schemes have been found to improve quality outcomes (4). For HIV/AIDS treatment in specific, there is evidence that inclusion and coordination between interprofessional healthcare teams that include specialties from infection control, specialized pharmacist and internist, can yield better outcomes (443). Pre-discharge reviews and improved post-discharge care, therefore, may prevent readmissions, although their cost-effectiveness is uncertain (1).

Another relevant finding of this work is that the random-effects term included in our model referring to unexplained factors specific to each hospital revealed apparent differences in the quality across the hospitals included in our study. In other words, 30-day readmission rate and LOS are still significantly higher in some hospitals in Portugal than in others. These unexplained factors can range from discrepancies in medical expertise, healthcare and clinical human resources. These findings warrant further discussions, such as how the CMI can affect the subsequent 30-day readmission or LOS. Moreover, special attention should assess how geographical location can affect the quality of care in Portugal.

Several entities and strategic documents call out loud for research on how to make health system measurement matter for policy and management. The WHO Regional Office for Europe, through the European Observatory on Health Systems and Policies, recommended the use of quality measures as an important method for sound policymaking and management (16). The Observatory encouraged European countries with public funding challenges to apply reforms that are motivated by the nominal objective of improving quality (16). Moreover, the observatory stated that on many occasions, "the data or analytical resources are not fit for

purpose; and in the absence of sound efficiency metrics, decision-makers may be tempted to implement crude expenditure reductions that indiscriminately affect both inefficient and efficient institutions and practitioners." A more reliable quality measurement and a more comprehensive understanding of how to analyze quality indicators are crucial for developing effective policies to improve the quality of care (16). The aims of this thesis are in line with Portugal's policy of cost reduction as a target to stabilize the economic situation and the Portuguese Court of Auditors, stating that the techniques used to analyze LOS within the DRG system is insufficient and is not done in the most appropriate manner (444).

There is a potential in policy decision-making concerning the optimal use of limited resources, and as a first step, this thesis investigated the determinants of 30-day readmission and LOS among HIV/AIDS patients in Portugal. We used robust methods to estimate the odds of 30-day readmissions and prolonged LOS. The approaches used here, with HIV/AIDS hospitalizations as the model, provide a framework of analysis for a growing population of HIV/AIDS patients, which can be further applied to other diseases and settings with similar characteristics. However, considering the methodological challenges generally encountered in estimating these quality indicators, this thesis also points to the need for more robust strategies to analyze these measures.

It is important to provide information to policymakers and health professionals concerning the burden of HIV/AIDS hospital admissions in the era of widespread ART access that prolong the life expectancy of HIV/AIDS patients and increase the cost of care overtime. Therefore, reporting the primary reasons for HIV-related readmission and the causes of prolonged LOS are important. This thesis takes a preliminary step towards assessing HIV/AIDS disease-specific hospital quality outcomes. Hospital quality estimates can support policy decision-making towards controlling HIV/AIDS health spending growth drivers and classifying hospitals in Portugal according to their performance. Moreover, with the future combination of such quality outcomes with disease-specific prevalence estimates, costing estimates and spending estimates, more precise targets can be constructed, and more disease-specific spending gaps could be identified.

Conclusions

Six main conclusions could be drawn from this thesis:

- This thesis contributes to attempts to reduce the economic burden of HIV/AIDS in Portugal and point to the importance of integrating quality measures such as a method for evaluating the performance of hospitals in light of limited resources.
- Findings from this thesis are supported by a large database that represents all Portuguese public HIV/AIDS admissions and can help develop a national health policy to avoid unnecessary readmissions or delayed discharges. These findings can also set the basis for new insights that can focus on patients at high risk of early readmissions or prolonged inpatient stays.
- The use of methods with low sensitivity to detect risk factors of quality measures, including study design, leads to a substantial underestimation of the actual outcomes. Precise associations were observed when these methodological limitations were overcome. The current work considered these concerns, which is in line with the recommendations by the Portuguese Court of Auditors, stating that the techniques used to analyze data within the DRG system are insufficient and are not done in the most appropriate manner. The statistical nature and distribution of quality measures require a deep understanding of the adopted statistical models to avoid biased estimates. The study of quality measures related to hospital performance, accounting for the nature of the data analyzed, to guarantee precise outcomes.
- The statistical methods that have been used in the thesis can be replicated and applied to other diseases and settings.
- Comorbidities and coinfections were confirmed as important risk factors for both early readmissions and prolonged LOS among HIV/AIDS hospitalizations in Portugal, and thus, must be considered in the overall patient care plan.
- This work revealed variability in the quality of hospitals through the variables included in the random-effects model, as 30-day readmission and prolonged LOS are still more frequent in some Portuguese hospitals than in others. These findings demand further investigations of the underlying causes and an analysis of any possible variations in the practices of hospitals that can be associated with greater rates of 30-day readmission and prolonged LOS.

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