AVAILABILITY OF ANTIRETROVIRAL DRUGS AND ASSOCIATED FACTORS: A COMPARISON BETWEEN MALTA AND NORWAY

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Abstract

Newer antiretroviral drugs (ARVs) are recommended as first line agents because they are more tolerable in terms of adverse events, and achieve faster viral suppression. Discontinuation of antiretroviral treatment(ART) due to adverse effects was shown to be 4% (16/414) in patients on newer ARVs, compared to 14% (58/419) in patients on older ARVs.[1] Following reports of limited availability of newer ARVs in Malta[2], the aim of this study was to compare the availability of ARVs in Malta to Norway, adherence to ARVs, and determine the factors associated with availability of ARVs. Malta and Norway have the same prevalence of HIV (0.1%) but different incidence rates. Malta reported an HIV incidence rate of 14.5 per 100,000 population in 2016 compared to 4.2 per 100,000 population in Norway.[2]

In this mixed-methods comparative cross-sectional study, data from the dispensing database at Mater Dei Hospital in Malta and the Norwegian Prescription Database was collected to determine the ARVs provided and the proportion of newer ARVs used in Malta and Norway. Using ARV refill dates from dispensing data, adherence to ART was determined using the proportion of days covered (PDC) method to investigate adherence as a factor associated with ARV availability. Using interviewer-administered questionnaires, face-to-face interviews were conducted with pharmacists in Malta and Norway responsible for ART provision to determine other factors associated with availability of ARVs.

ART was provided free of charge by the national health services in Malta and Norway. Up to 23.4% (N= 38605) of ARV prescriptions in Norway were for newer ARVs, compared to 4.9% of all prescriptions (N= 5657) in Malta. Patients in Malta and Norway showed comparable levels of adherence to ART. Seventy one percent (N=3991) of patients in Norway and 74% of patients (N= 265) in Malta had the desired adherence level at a PDC $\geq$ 95.0%. The 3 pharmacists involved in ART provision in Malta reported that challenges hampering availability of newer ARVs included an out-dated formulary, challenges in drug forecasting, and absence of HIV-allocated funding.

In Norway and Malta, the high cost of ARVs compounded by the small market size affected provision of ARVs. Notwithstanding the high cost of ARVs, willingness-to-pay by the national health system was higher in Norway than in Malta. Pre-exposure prophylaxis (PrEP) was provided free of charge in Norway, and not provided in Malta. Interview respondents in Norway reported that the political will to provide the current standard of ART was high, while interview respondents in Malta reported the opposite.

Norway spends more money on ART, which could explain the higher availability of the newer more expensive ARVs as well as PrEP in Norway. Malta spends €4.5 per capita and 2.8% (€1.8 million) of the national pharmaceutical expenditure on ART, while Norway spends €12.26 per capita and 5.2% (€61,316,302) of the national pharmaceutical expenditure on ART. Increasing expenditure on ARVs, and providing newer ARVs and PrEP in Malta could reverse the increasing trend of HIV incidence in Malta.

Keywords: antiretroviral drugs, antiretroviral therapy, availability, Europe, human immunodeficiency virus, Malta, Norway

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[2] Fast-tracking the end of AIDS in Europe – practical evidence-based interventions. European Centre for Disease Prevention and Control. Valletta; 2017 [Cited 2017 Feb 20]. Available at https://www.eu2017.mt/Documents/Media%20Advisory%20Note/HIV%20Conference%20Programme.pdf

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3TC	Lamivudine
AIDS	Acquired Immunodeficiency Deficiency Syndrome
ATC	Anatomical Therapeutic Chemical Classification
ART	Antiretroviral Therapy
ARVs	Antiretroviral drugs
CPSU	Central Procurement and Supplies Unit
EACS	European AIDS Clinical Society
ECDC	European Center for Disease Prevention and Disease Control
EEA	European Economic Area
EU	European Union
HAART	Highly Active Antiretroviral Therapy
FTC	Emtricitabine
GP	General Practitioner
HAART	Highly Active Antiretroviral Therapy
HCP	Health Care Professional
HIV	Human Immunodeficiency Virus
INI	Integrase inhibitor
INRUD	International Network for Rational Use of Drugs
MDH	Mater Dei Hospital
MPR	Medication Possession Ratio
MSM	Men who have sex with men
MTR	Multiple Tablet Regimen
NIS	National Insurance Scheme
NorPD	Norwegian Prescription Database
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PDC	Proportion of days covered
PI	Protease inhibitor
PBS	Pharmaceutical Benefit Scheme
PLWHIV	People Living With HIV
PrEP	Pre-exposure prophylaxis

STR	Single Tablet Regimen
TasP	Treatment as Prevention
TCM	Thiacytidine Medication
TDF	Tenofovir
UK	United Kingdom
UNAIDS	United Nations Joint Programme on HIV/AIDS
WHO	World Health Organisation

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CHAPTER 1

INTRODUCTION

Chapter 1: Introduction

1.1 HIV in Europe

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) continues to be a public health concern in Europe. While the number of new cases of HIV infection has been decreasing in certain parts of the world with the greatest burden of disease, other regions are showing an upward trend, such as Eastern Europe, the Middle East, North Africa, Central Asia and the Central European region (Gökengin et al., 2016).

According to the European Centre for Disease Prevention and Control (ECDC), 29444 individuals were diagnosed with HIV in the European Union/ European Economic Area (EU/EEA) in 2016, with a rate of 5.9 per 100,000 population. Countries with the highest rates of new HIV diagnoses reported in 2016 per 100,000 population were Latvia (18.5 per 100,000 population), Estonia (17.4 per 100,000 population), and Malta (14.5 per 100,000 population). The lowest rates were reported by Slovakia (1.6 per 100,000 population) and Hungary (2.3 per 100,000 population). [1]

The global trend has shown a decline in new HIV infections, but the incidence of HIV has been stable in some regions of Europe, and increased in others.[2] Over the past decade

[1] European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2017 – 2016 data [Internet]. Stockholm: ECDC; 2017 [Cited 2017 Dec 12]. Available from https://ecdc.europa.eu/sites/portal/files/documents/20171127-Annual_HIV_Report_Cover%2BInner.pdf.

[2] Joint United Nations Programme on HIV/AIDS. AIDS by the numbers 2016. UNAIDS 2016 [Cited 2018 Jan 15]. Available from http://www.unaids.org/sites/default/files/media_asset/AIDS-by-the-numbers-2016_en.pdf

Europe has had little fluctuation in the rate of HIV diagnoses per 100,000 population, and in the past several years it has only declined from 6.9 per 100,000 population in 2008 to 6.3 per 100,000 population in 2015, and down to 5.7 in 2016.[3]

HIV is a blood-borne virus that can be transmitted horizontally or vertically. In horizontal transmission, also known as secondary transmission, transfer of the virus mainly occurs through sexual intercourse, or needle sharing. Vertical transmission involves the transfer of HIV from mother to child during pregnancy, child birth or breast-feeding.[4] The most prevalent mode of transmission of HIV in Europe is sex between men, which accounts for over 50% of new infections. This is closely followed by heterosexual transmission, and transmission through injectable drug use.[5]

As the immune system declines due to impairment by the virus, HIV infection can progress to AIDS. AIDS is characterised by conditions and opportunistic infections that normally would not be present in individuals without a compromised immune system. These AIDS-defining illnesses, such as cryptococcal meningitis and Kaposi's sarcoma, are observed in individuals without successful viral suppression while on antiretroviral

[3] European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2017 – 2016 data [Internet]. Stockholm: ECDC; 2017 [Cited 2017 Dec 12]. Available from https://ecdc.europa.eu/sites/portal/files/documents/20171127-Annual_HIV_Report_Cover%2BInner.pdf

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[5]European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2017 – 2016 data. Stockholm: ECDC; 2017 [Cited 2017 Dec 12]. Available from https://ecdc.europa.eu/sites/portal/files/documents/20171127-Annual_HIV_Report_Cover%2BInner.pdf.

therapy (ART) and in individuals diagnosed with HIV at an advanced stage (Babiker et al., 2013).

Almost half of new HIV diagnoses (48%) in Europe are late diagnoses [6], also known as delayed presentation. Delayed presentation occurs when HIV infected individuals present for diagnosis with a CD4 cell count less than 350 cells/mm (Guaraldi et al., 2017). Individuals unaware of their HIV status are at risk of delayed presentation and pose a risk of passing on the infection. Delayed presentation also increases the risk for polypharmacy, non-adherence, opportunistic infections, and HIV-related mortality (Camoni et al., 2013).

Recognising the need for concerted efforts to end HIV, European and Central Asian countries met during the Irish EU Council Presidency in 2004 and adopted the Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia. The declaration comprises 33 statements on breaking the barriers to ending HIV, described under 4 themes: leadership, prevention, partnership and follow-up. The ECDC has been monitoring the implementation of this declaration since 2009.[7]

In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) set the 90-90-90 targets in an effort to eradicate HIV/AIDS by 2030. UNAIDS envisages that by 2020,

[7] World Health Organisation Regional Office for Europe. Dublin declaration on partnership to fight HIV/AIDS in Europe and Central Asia [Internet]. Dublin: WHO; 2004 [Cited 2018 Jun 05]. Available from http://www.euro.who.int/en/health-topics/communicable-diseases/hivaids/policy/guiding-policy-documents-and-frameworks-for-whoeuropes-work-on-hiv/dublin-declaration-on-partnership-to-fighthivaids-in-europe-and-central-asia.

90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will have received sustained ART and 90% of all people receiving ART will have viral suppression. If these targets are achieved, then it is believed that HIV will be eradicated by 2030.[8]

1.1.1 HIV in Malta

In 2016, Malta was one of the three countries that reported the highest rate of HIV incidence in Europe, at a rate of 14.5 per 100,000 population. [9] According to surveillance data reported by ECDC, the incidence of HIV in Malta has increased steadily over the past 5 years, from 7.2 in 2012 to 14.5 in 2016. Over 60% of the new transmissions were among men who have sex with men (MSM), and over 60% of new diagnoses were among the age group 30 – 39 years.

Over half of new diagnoses were among people originating from outside the country. For newly diagnosed patients, the region of origin at diagnosis was reported as Malta for 25.4%, Western Europe (30.2%), Central and Eastern Europe (14.3%) and Sub-Saharan Africa (15.9%).[8] As of 2016, the number of HIV diagnoses in Malta was reported by the ECDC as being 387, which is approximately 0.1% of the population.

[8] Joint United Nations Programme on HIV/AIDS. 90-90-90 An ambitious treatment target to help end the AIDS epidemic [Internet]. UNAIDS; 2014 [Cited 2017 Feb 09]. Available from http://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf

[9] European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2017 – 2016 data [Internet]. Stockholm: ECDC; 2017 [Cited 2017 Dec 12]. Available from https://ecdc.europa.eu/sites/portal/files/documents/20171127-Annual_HIV_Report_Cover%2BInner.pdf.

1.1.2 HIV in Norway

In 2015, Norway reported its greatest decline in new HIV diagnoses in 10 years, from a rate of 5.3 per 100,000 population in 2007, peaking at 6.3 per 100,000 population in 2008, then down to 4.3 per 100,000 population in 2015. The greatest decline was reported in MSM. From 2015 to 2016, the number of new diagnoses was stable, at 221 in 2015 and 220 in 2016. [10] Table 1.1 shows a comparison of HIV incidence between Malta and Norway.

As was the case in Malta, over half of new diagnoses in Norway in 2016 were among people originating from outside Norway. For newly diagnosed patients, the region of origin was reported as Norway for 40.5%, 6.4% for Western Europe, 6.4% for Central and Eastern Europe and 24.5% for Sub-Saharan Africa.[11]

Table 1.1 Rates of new HIV diagnoses per 100,000-population by country and year of diagnosis

Country	Year				
	2012	2013	2014	2015	2016
Malta	7.2	8.5	9.4	14.2	14.5
Norway	4.9	4.6	5.2	4.3	4.2

[10] Decline in HIV cases in Norway in 2015 [Internet]. Norwegian Institute of Public Health; 2016 [Cited 06/07/2017]. Available from https://www.fhi.no/en/news/2016/HIV-2015/

[11] European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2017 – 2016 data [Internet]. Stockholm: ECDC; 2017 [Cited 2017 Dec 12]. Available from https://ecdc.europa.eu/sites/portal/files/documents/20171127-Annual_HIV_Report_Cover%2BInner.pdf.

1.2 Antiretroviral therapy

The primary goals of antiretroviral therapy (ART) are to suppress viral replication and preserve and restore the number of circulating CD4+ T cells, the immune cells attacked by HIV (Patel et al., 2014). There are more than 30 antiretroviral pharmaceuticals available for the treatment of HIV infection (Schmidt et al., 2015).

1.2.1 Treatment of HIV infection

The treatment regimen usually comprises a combination of at least three drugs, referred to as Highly Active Antiretroviral Therapy (HAART). With effective treatment, HIV is no longer a death sentence, and has become a manageable chronic condition (Treskova et al., 2016). Treatment for HIV has been available in Europe since the 1990s (Camoni et al., 2013) and HAART has improved the quality of life and life expectancy of people living with HIV (PLWHIV) (Trapero-Bertran et al., 2014). As of June 2017, 20.9 million people were accessing ART globally.[12]

Current guidelines recommend starting ART as soon as a patient is diagnosed as HIV positive (Barnhart et al., 2017). Previous guidelines recommended that ART should be started at a CD4 count of 350 cells/μL or less (Jain and Deeks, 2010). Following evidence that showed that starting ART early reduced morbidity, improved outcomes and lowered the risk of HIV transmission, guidelines were issued to start ART immediately upon a positive a diagnosis (Eholie et al., 2016).

[12] Joint United Nations Programme on HIV/AIDS. Latest statistics on the status of the AIDS epidemic [Internet]. UNAIDS 2018; [Cited 2018 Sept 15]. Available at http://www.unaids.org/en/resources/fact-sheet

ART regimens usually comprise a combination of three antiretroviral drug classes consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) and a third agent, either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor (INI), recommended as first-line therapy (Schmidt et al., 2015). It is recommended that first-line NRTI combinations contain an element of a thiacytidine medication (TCM), either lamivudine (3TC) or emtricitabine (FTC). The two medications are interchangeable, but because of their high antiretroviral similarity, concomitant use is avoided as it does not confer additional benefits. NRTI-free regimens such as PI monotherapy are not recommended because of inferior antiviral potency (McCoy et al., 2018).

Currently, patients can access ART as single-tablet regimens (STRs) and newer fixed-dose combination (FDC) tablets, which gives patients more options for selecting an ARV regimen, fewer adverse effects and better tolerability and clinical outcomes (McCoy et al., 2018). Even though current guidelines recommend a 3-drug regimen, in an effort to maximise the above four benefits, there has been interest in using a 2-drug regimen and whether a regimen with fewer drugs could achieve viral suppression. A recent study found that this can be achieved; a combination treatment of dolutegravir and rilpivirine achieved non-inferior viral suppression compared to a three- or four-drug regimen (Patel et al., 2014).

Newer STRs include dolutegravir/lamivudine/abacavir (Triumeq), rilpivirine/emtricitabine /tenofovir alafenamide (Odefsey), rilpivirine/emtricitabine/tenofovir disoproxil fumarate (Complera),

elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild), and elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide (Genvoya). Other recently approved FDCs are atazanavir/cobicistat (Evotaz), darunavir/cobicistat (Prezcobix), and emtricitabine/tenofovir alafenamide (Descovy) (McCoy et al., 2018). Table 1.2 shows the drugs used for the treatment of HIV.

Alongside ART, numerous strategies have been put in place that can bring about the end of the AIDS epidemic by 2030 and to achieve this, early ART has to be scaled up as late treatment would only allow the epidemic to continue to outpace the response (Sidibé et al., 2016).

1.2.2 HIV treatment as prevention and pre-exposure prophylaxis

The ability of ART to decrease the risk of HIV transmission has been demonstrated in observational studies (Del Romero et al., 2010) and a randomised controlled trial (Cohen et al., 2016). The randomised controlled trial showed that the transmission of HIV was decreased by 96% in sero-discordant couples. The results of this trial led to the development of new ART guidelines that recommended starting ART early and at a high CD4 threshold, and providing pre-exposure prophylaxis (PrEP) to limit transmission of HIV (Cambiano et al., 2013).

Effective ART is one of the most valuable strategies of HIV prevention and elimination (Cohen et al., 2016; Card et al., 2017), as ART has been shown to decrease transmission of HIV (Siedner et al., 2014). The concept of providing ART to HIV positive individuals to limit transmission to HIV-negative partners is referred to as treatment as prevention

(TasP) (Grant RM. et al., 2010). PrEP, post exposure prophylaxis and Prevention of Mother to Child Transmission (PMTCT) are forms of treatment as prevention (TasP). TasP is a two-pronged strategy: 1) HIV negative individuals at high risk of contracting the virus can be prescribed ART as a prophylactic measure, and 2) when HIV positive patients on ART achieve sufficient viral suppression their risk of transmitting the virus is greatly (Cambiano et al., 2013).

Table 1.2 Drugs used for the treatment of HIV

Single-Tablet Regimens	**Nucleoside/Nucleotide Reverse Transcriptase Inhibitors**
• Efavirenz + tenofovir disoproxil fumarate + emtricitabine • Bictegravir + tenofovir alafenamide + emtricitabine • Rilpivirine + tenofovir disoproxil fumarate + emtricitabine • Elvitegravir + tenofovir alafenamide + emtricitabine + cobicistat • Dolutegravir + rilpivirine • Rilpivirine + emtricitabine + tenofovir alafenamide • Elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine • Dolutegravir + abacavir + lamivudine	• Zidovudine + lamivudine • Emtricitabine + tenofovir alafenamide • Emtricitabine • Lamivudine • Abacavir + lamivudine • Zidovudine • Abacavir + zidovudine + lamivudine • Tenofovir disoproxil fumarate + emtricitabine • Didanosine • Tenofovir disoproxil fumarate • Stavudine • Abacavir
Protease Inhibitors	**Non-nucleoside reverse transcriptase inhibitors**
• Tipranavir • Indinavir • Atazanavir + cobicistat • Saquinavir • Lopinavir + ritonovir • Fosamprenavir • Ritonavir • Darunavir + cobicistat • Darunavir • Atazanavir • Nelfinavir	• Rilpivirine • Etravirine • Delavirdine • Efavirenz • Nevirapine and Nevirapine XR
	Pharmacokinetic enhancers
	Cobicistat (not an antiretroviral)
Entry inhibitors	**Integrase inhibitors**
• Enfuvirtide • Maraviroc	• Raltegravir • Dolutegravir • Elvitegravir

The risk of transmission was found to be zero when a patient's viral load falls below 400 copies/mL (Attia et al., 2009). ART was found to lower the risk of HIV transmission over a median of 3.5 years of observation time, and sustainably reduce the risk of transmission to greater than 90% by providing viral suppression to undetectable levels (Siedner et al., 2014). TDF has also been shown to have a high genetic barrier to resistance (Etiebet et al., 2013) and achieved particularly high concentrations in rectal mucosa, which could provide a protective effect to HIV transmission through anal intercourse among MSM and heterosexual women (Krakower et al., 2015). The nucleoside reverse transcriptase inhibitor emtricitabine (FTC) also showed an excellent safety profile and achieved high concentrations in the female genital tract (Dumond et al., 2007).

Amounting evidence prompted the recommendation for PrEP in sero-discordant couples and other individuals at great risk of acquiring HIV (Muessig and Cohen, 2014). Daily oral PrEP with a fixed-dose combination of TDF and FTC has been shown to be safe, well-tolerated and efficacious in significantly decreasing HIV incidence in high-risk individuals (Krakower and Mayer, 2015). PrEP was shown to reduce the incidence of HIV, especially when used with behavioural preventive measures (Tetteh et al., 2017). Individuals at high risk of HIV infection include men who have sex with men (gay and bisexual men), transgender people, female sex workers, injectable drug users and sero-discordant couples (Okal et al, 2013).

1.3 HIV Treatment in Malta

In Malta, health care delivery follows a universal coverage model. It is centrally organised and is delivered mainly through a National Health Service that is funded largely through

taxation and public expenditure. Medicines are free at source and co-payments are not required (Azzopardi-Muscat et al., 2017). Antiretroviral medicines are free for diagnosed patients legally resident in Malta.

HIV treatment in Malta is centralised in structure. Medical care is provided by specialists at the state general hospital, Mater Dei Hospital, and patients are seen periodically to monitor their therapy. Patients obtain the ARV medication from a sole pharmacy at the state general hospital. Other medication, including HIV-related medication can be obtained from a pharmacy of the patient's choice. The prescriptions are then reimbursed by the national health insurance accordingly. While prescription records are paper-based, an electronic record is kept of every dispensing encounter.

1.4 HIV Treatment in Norway

The health care system in Norway is also based on universal health care (Ringard et al., 2013). All citizens have membership to the Norwegian National Insurance Scheme that is largely funded by a public third party payer. There is a pharmaceutical benefit scheme (PBS) in place, and all patients with a national identification number can buy medicines through the PBS. There is a co-payment structure in place, however under the PBS, there is a special track in which drugs for certain infectious diseases (such as HIV/AIDS and tuberculosis) are provided free of charge in Norway (Håkonsen et al., 2015).

HIV treatment in Norway is decentralized in structure. All aspects of management including diagnosis, treatment and follow-up are considered to be an integrated part of

both the primary health care and specialist services at both the municipal and county levels.[13] Routine medical care for HIV patients is provided by the regular primary health physician, and patients are referred to specialists only when necessary. Patients collect their prescribed antiretroviral medicines from a community pharmacy of their choice.

1.5 Adherence to antiretroviral therapy

Patient adherence refers to the degree to which patients follow their therapeutic regimen as prescribed within a set period of time (Murphy et al., 2012). Adherence to ART is a major factor in the success of HIV treatment. ART adherence is of such great importance that it is the second leading predictor of progression of HIV to AIDS and death, after CD4 count (Golin et al., 2002). A patient who is not adherent to ART on a triple drug regimen has an almost 4 times greater likelihood of mortality than a patient who is adherent on the same drug regimen (Paterson et al., 2000).

In order to limit treatment failure and viral resistance, levels of adherence of 95% are required (Weiser et al., 2003). Adherence to ART correlates greatly to treatment failure, and it has been shown that even an adherence of more than 95.0% can result in 22.0% virologic failure, while adherence levels between 80.0% and 95% can lead to 61.0% treatment failure and adherence of less than or equal to 80.0% can lead to a treatment

[13] Norwegian Ministry of Health and Care Services. HIV Prevention in Europe: A Review of Policy and Practice. Norwegian Country Report [Internet]. Ministry of Health and Care Services; 2000 [Cited 2017 Apr 04]. Available at https://www.regjeringen.no/en/dokumenter/hiv-prevention-in-europe-a-review-of-pol/id420032/

failure of 80.0%.[14] With the right treatment regimen and optimum adherence, viral suppression can be achieved resulting in prolonged life for the patient, better quality of life and a greatly reduced risk of transmitting the virus (Cambiano et al., 2013).

There is no gold standard for measuring adherence (Anuradha et al., 2011), and various approaches are used. Adherence can be measured directly or indirectly. Direct measurements include observed therapy and measurement of metabolite concentrations (Iuga et al., 2014). Indirect methods are more frequently used, and these include patient self-report, pill counting, dose-counting devices, electronic prescribing, patient keeping appointments at clinic visits, and pharmacy records (Iuga et al., 2014).

Two other indirect methods of measuring adherence are the medication possession ratio (MPR) and the proportion of days covered (PDC). To calculate MPR, the total number of days of medicine supplied is divided by the number of days between the first and last refills; while PDC is calculated by dividing the total number of days of medicine supplied during an interval by the total number of days during that interval (LaFleur and Oderda, 2004).

The MPR and PDC methods make use of routine pharmacy data and work best in health facilities with good record keeping. Pharmacy records have been used as a means of measuring adherence to ART as routine pharmacy records on prescription refills are easy to obtain at a relatively low cost and are not subject to recall bias (Grimes et al., 2013).

[14] UNAIDS/WHO. AIDS epidemic update [Internet]. Geneva: UNAIDS, World Health Organization; 2011 [Cited 2017 May 11]. Available from http://www.unaids.org/sites/default/files/media_asset/20111130_UA_Report_en_1.pdf

Direct methods of measuring adherence are more accurate but are also more resource intensive.

Factors that affect adherence can be divided into patient-related factors - such as age, sex, education, income, mental illness, social support system - and health provider-related factors, and external factors (Iuga et al., 2014). Availability of ARVs is a health-provider related factor that can affect ART adherence.

In addition to the patient-related positive outcomes, optimal ART adherence has been associated with health system related positive outcomes (Munakata et al., 2006). Adherence to ART leads to fewer hospital readmissions and reduced costs (Nosyk et al., 2006) since patients that are adherent are at a lower risk of treatment failure and opportunistic infections (Wang et al., 2009). One study found that patients with consistent adherence had a reduced utilisation of medical resources resulting from decreased number of non-trauma hospitalisations, shorter hospital stays, and lower hospitalisation expenses.

Efforts to increase access to ARVs have rightly been focused on providing more affordable drugs, either at subsidised rates or free of charge, however the benefit of ART cannot be fully realised if ART is not correctly implemented. It is important to investigate patient adherence to ensure positive treatment outcomes.

1.6 Cost of antiretroviral therapy

Following the WHO guidelines to start ART for all newly diagnosed individuals (Barnhart, 2017), the need to scale up treatment continues to rise with the increase of new HIV diagnoses in Europe. The challenge then becomes the cost of availing antiretroviral therapy to an increasing population of People Living with HIV (PLWHIV) (Waning et al., 2010).

Provision of HIV healthcare is expensive (Gebo et al., 2010), and the most expensive aspect of HIV management is the cost of ART (Treskova et al., 2016). A review of the economic impact of HIV care in five European countries found that the treatment cost ranged from €6,399 (SD €2,503) per patient per year in Italy to €32,110 (SD €6,960) per patient per year in Germany, and costs were higher for first-line therapy than for second- and third-line regimens (Trapero-Bertran and Oliva-Moreno, 2014).

Newer ARVs have been shown to be tolerable in terms of adverse events, and they achieve faster viral suppression (McCoy et al., 2018). Discontinuation of antiretroviral treatment(ART) due to adverse effects was shown to be 4% (16/414) in patients on newer ARVs, compared to 14% (58/419) in patients on older ARVs (Walmslsey et al., 2015). Newer ARVs are however more expensive (Waning et al., 2010) than older ARVs, which may hamper the ability of health care systems to effectively supply newer regimens.

Integration of PrEP into national HIV programmes that include increased testing, early treatment for diagnosed individuals and combination HIV prevention has contributed to

a reduction in new HIV infections (Coleman and Prins, 2017). However, the high cost of ARVs has hindered some countries from availing free PrEP. Norway and Scotland, have integrated PrEP into the national HIV programmes and it is provided free to all at-risk individuals (Coleman and Prins, 2017). Other countries, such as France provide PrEP at a subsidised cost (McCormack et al, 2016).

1.7 Disparity in HIV treatment across Europe

There exists a disparity in provision of HIV care between the European countries, with Northern Europe faring better than other regions (Lazarus et al., 2016). There is also a disparity in pharmaceutical expenditure across Europe. This disparity can be attributed to different factors, primary of which is national income per capita. Malta's income per capita in 2016 (adjusted by purchasing power parity) is USD 35,720 while that of Norway was USD 62,510.[15] When it comes to procuring pharmaceuticals, prices of pharmaceuticals are higher in European countries with higher income per capita, and higher income countries spend more on pharmaceuticals.[16]

Population size is another factor associated with the disparity in HIV care across the nations of Europe. Population size determines market size for pharmaceuticals, and is closely linked to the willingness of pharmaceutical countries to penetrate the market and

[15] World Bank. Development Indicators Database [Internet]. World Bank; 2016 [Cited 2017 Mar 18]. Available from https://data.worldbank.org/products/wdi

[16] Kanavos P, Vandoros S, Irwin R, Nicod E, Casson M. Differences in cost and access to pharmaceutical products in the EU. Brussels: European Parliament, Directorate General for Internal Policies; 2011 [Cited 2017 Aug 27]. Available from http://www.europarl.europa.eu/RegData/etudes/etudes/join/2011/451481/IPOL-ENVI_ET(2011)451481_EN.pdf.

make their products more easily accessible. Smaller populations conversely have a smaller consumption of pharmaceuticals, and this means less profit for the pharmaceutical companies, taking away their incentive to penetrate small markets.

Malta is considered a small pharmaceutical market[17] and Norway is comparable in this regard (Hågå et al., 2002). Malta is an island state with a population of 400,000 and Norway has a population of 5 million. The prevalence of PLWHIV is 0.1% of the general population in both countries.

While prices of antiretroviral drugs have seen a downward trend in developing countries, advocated for by civil society and non-governmental groups (Geffen, 2017) and resulting in increased affordability and access to antiretroviral drugs in these countries, middle income and developed countries have not benefited as much from similar antiretroviral price reductions.[18]

Pharmaceutical companies base the price of ARVs on the GDP of the country and the burden of the epidemic. This means that lower income, highly endemic regions can receive ARVs at affordable prices. This is a desirable outcome; however, it means that

[17] World Health Organisation. Enhancing access to affordable medicine in small countries. Fourth High-level Meeting of Small Countries in Malta. World Health Organisation; 2017 [Cited 2017 Nov 10]. Available from http://www.euro.who.int/en/countries/malta/news/news/2017/07/enhancing-access-to-affordable-medicine-in-small-countries

[18]IRIN Guardian Development Network. HIV and AIDS: bad news for drug prices in middle-income countries [Internet]. In: The Guardian; 2011 [Cited 2017 Nov 15]. Available from https://www.theguardian.com/global-development/2011/jul/22/hiv-aids-antiretroviral-drugs-pricing

middle income and developed countries continue to pay highly for ARVs. The cost is a major limiting factor in the provision of antiretroviral drugs.

According to the ECDC report of the expert meeting on "Fast tracking the end of AIDS in Europe" held in Valletta in January 2017, the pricing and affordability of ARVs has been a major barrier to treatment, and has to be addressed as a priority at EU level. Suggestions on how to tackle this included joint procurement mechanisms and multi-country negotiations with pharmaceutical companies.[19]

1.8 Rationale for the study

Reports indicate that Malta lacks availability of the newer guideline recommended ARVs.[18] This is also supported by anecdotal accounts from health care professionals in Malta. Newer ARVs are those that were approved from 2005 onwards, including new drugs within the conventional classes, such as the NNRTIs etravirine and rilpivirine; the second-generation protease inhibitors darunavir and tipranavir; and the drugs in the new drug classes - maraviroc, an entry inhibitor, and raltegravir, the first integrase inhibitor to be approved. Other integrase inhibitors include dolutegravir and elvitegravir (Bayoumi et al., 2013). Newer ARVs are more tolerable for patients in terms of adverse events, and achieve faster viral suppression (McCoy et al., 2018).

Malta has attained the second of the 3 UNAIDS 90-90-90 targets, and is well on the way to achieving the third.[18] Achievement of these targets relies on a stronger focus on HIV

[19] Fast-tracking the end of AIDS in Europe – practical evidence-based interventions. European Centre for Disease Prevention and Control. Valletta; 2017 [Cited 2017 Feb 20]. Available at https://www.eu2017.mt/Documents/Media%20Advisory%20Note/HIV%20Conference%20Programme.pdf

prevention (Sidibé, 2016). Treatment of HIV/AIDS is a key strategy of prevention, as effective treatment reduces the risk of transmission of the virus to non-infected persons in addition to prolonging the survival of patients (Cambiano, 2013).

Antiretroviral therapy is one of the costliest aspects of HIV treatment (Waning et al., 2009) and the cost of medicines is an important factor in determining availability of medicines. Newer ARVs have been found to be safer and more tolerable than older drugs, and achieve faster viral load suppression, however newer ARVs are also more expensive than other ARVs (McCoy et al., 2018). To achieve the full benefit of treatment as prevention, sustained availability of the expanded options of guideline recommended antiretroviral drugs is needed.

There is evidence to suggest that when a limited number of ARVs is available, first line agents may be restricted to second line use, to preserve the options available to prescribers and patients in case of treatment failure. As a result, patients may suffer from more side effects (Toverud et al., 2012).

Current antiretroviral treatments can reduce HIV-associated morbidity and prolong survival (Cihlar et al., 2016). Further, availability of highly active antiretroviral therapy has been shown to reduce the number of HIV-related hospitalisations (Mahlab-Guri et al., 2017). This means health care costs are reduced when the appropriate medication is available.

Since the approval of the first ARV, more than 30 antiretroviral pharmaceuticals are available for the treatment of HIV infection (Broder, 2010). Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are still the main components of antiretroviral drug combinations (Cihlar and Fordyce, 2016) and are recommended as an element of any first-line antiretroviral regimen by therapy guidelines (Richardson et al., 2014; Cihlar and Fordyce, 2016).

HIV treatment is constantly evolving and dolutegravir-containing regimens are currently recommended as the most successful in suppressing the virus and are better tolerated by patients. Dolutegravir is a newer ARV and the price of newer drugs remains prohibitively high. The price of dolutegravir, and other salvage line treatments like raltegravir remains high because of the lack of quality-assured generics. [20] Such access issues can hinder effective management of HIV when the cost of medicines is a limiting factor.

The factors associated with the limited availability of the newer recommended antiretroviral drugs on PLWHIV in Malta have not been characterized in published literature. This researcher found no previous studies comparing availability of antiretroviral drugs between Malta and other European countries, nor studies describing the factors associated with ARV availability in Malta.

[20] Medicins Sans Frontieres. Untangling the Web of Antiretroviral Price Reductions [Internet]. Medicins Sans Frontieres; 2014 [Cited 2017 July 16]. Available at https://www.msfaccess.org/sites/default/files/MSF_UTW_17th_Edition_4_b.pdf

In addition to the absence of published literature and the disparity in HIV care that exists between European nations, a number of other characteristics support a comparative study between Malta and Norway. The two countries are comparable in terms of both being small markets and having a similar proportion of the population living with HIV/AIDS, that is 0.1%.[21] However, in 2016 the Norwegian Institute of Public Health reported the lowest number of new HIV cases observed in the past decade, while Malta observed a steady upward trend. It is prudent to compare ARV availability in Malta to that in a country that is reporting improvements, such as Norway. Acquiring information on the HIV population, and the management of HIV, is of both public health and economic importance (Schmidt et al., 2015).

1.9 Aims of the study

The aims of this study were to:

1) To compare the availability of antiretroviral drugs between Malta and Norway
2) To compare patient adherence to antiretroviral drugs between Malta and Norway
3) To determine the factors associated with availability of antiretroviral drugs in Malta and Norway

[21] European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2017 – 2016 data [Internet]. Stockholm: ECDC; 2017 [Cited 2017 Dec 12]. Available from https://ecdc.europa.eu/sites/portal/files/documents/20171127-Annual_HIV_Report_Cover%2BInner.pdf.

CHAPTER 2:

METHODOLOGY

Chapter 2: Methodology

2.1 Overview

This study used a mixed methods comparative approach and cross-sectional design. Two tools were used to collect data. A data sheet was used in a quantitative methods approach to collect data from dispensing databases and determine the antiretroviral drugs (ARVs) dispensed to patients, the number of patients receiving each antiretroviral regimen, and to determine adherence. A key informant interview questionnaire was used in a qualitative methods approach, to investigate the issues surrounding availability of ARVs and explain the observed patterns of ARV availability in Malta and Norway. The study was conducted between January and December 2017. Figure 2.1 gives an overview of the study.

2.2 Literature search

A literature search was conducted to establish the current status of Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) in Malta, Norway, and Europe in general, and to establish what research has been conducted in the field of availability of antiretroviral drugs in Europe, Malta and Norway. PubMed and the HyDi University of Malta library database were searched using the topics in Figure 2.2. An online search was also conducted for official government documents on the management of HIV/AIDS in Malta and Norway.

2.3 Ethical approval and institutional permissions

Permission to conduct the study was sought and obtained from the University Research Ethics Committee of the University of Malta, and the Data Protection Officer and Administration of Mater Dei Hospital (Appendix 1). Permission was granted by the Norwegian Institute of Public Health (Appendix 2) to obtain and use data from the Norwegian Prescription Database (NorPD). Use of anonymous data from the NorPD for research did not require ethics review board permission.[22] To maintain patient confidentiality all data obtained from the databases was anonymous, and did not contain any identifying information.

2.4 Identifying key participants and sources of data

Key participants were identified in both Malta and Norway to determine the data sources and how data collection would be conducted.

2.4.1 Stakeholders and study participants in Malta

The Central Procurement and Supplies Unit is the body responsible for procuring medicines at Mater Dei Hospital, and Mater Dei Hospital is the only source of ARVs for all HIV patients in Malta using the public health care system. For this reason, collection of data on dispensing of ARVs was limited to Mater Dei Hospital.

[22] Legal requirements. Access to data from the Norwegian Prescription Database [Internet]. Norwegian Institute of Public Health; 2017. Cited on 11/06/2017 Available at https://www.fhi.no/en/op/data-access-from-health-registries-health-studies-and-biobanks/norwegian-prescription-database/Access-data-norpd/

The stakeholders and study participants identified in Malta were the clinical health care team at the infectious diseases department of Mater Dei Hospital who are responsible for providing ART, and the pharmacy dispensing team. The clinical team comprises two infectious diseases physicians, one clinical pharmacist and a nurse. The dispensing team comprises two pharmacists.

The infectious diseases consultants and the clinical pharmacist were contacted via electronic mail, inviting them to participate in the study. Two face-to-face meetings were conducted with them to establish feasibility of the study. One meeting was held with the clinical pharmacist alone, and the second meeting was held with both the clinical pharmacist and the infectious diseases consultant together. The health care professionals read the study protocol and provided feedback on the feasibility of the study. Patient confidentiality was a key factor in determining the feasibility of this study. In the meeting with the infectious disease consultant and clinical pharmacist it was ascertained that prescriptions handed to patients and pharmacy dispensing records do not contain patient names, and anonymising codes were used instead.

Another important aspect identified during the discussion on feasibility was that participants to be interviewed during data collection would be pharmacists and not the physicians, as pharmacists were more directly involved with drug availability issues than physicians. The clinical team emphasised that the major gap in antiretroviral care in Malta is limited availability of newer antiretroviral drugs, as opposed to a general ARV shortage. With this in mind, the data collection tools were designed to identify which drugs are in use, and why there is a difference in availability of the various drugs.

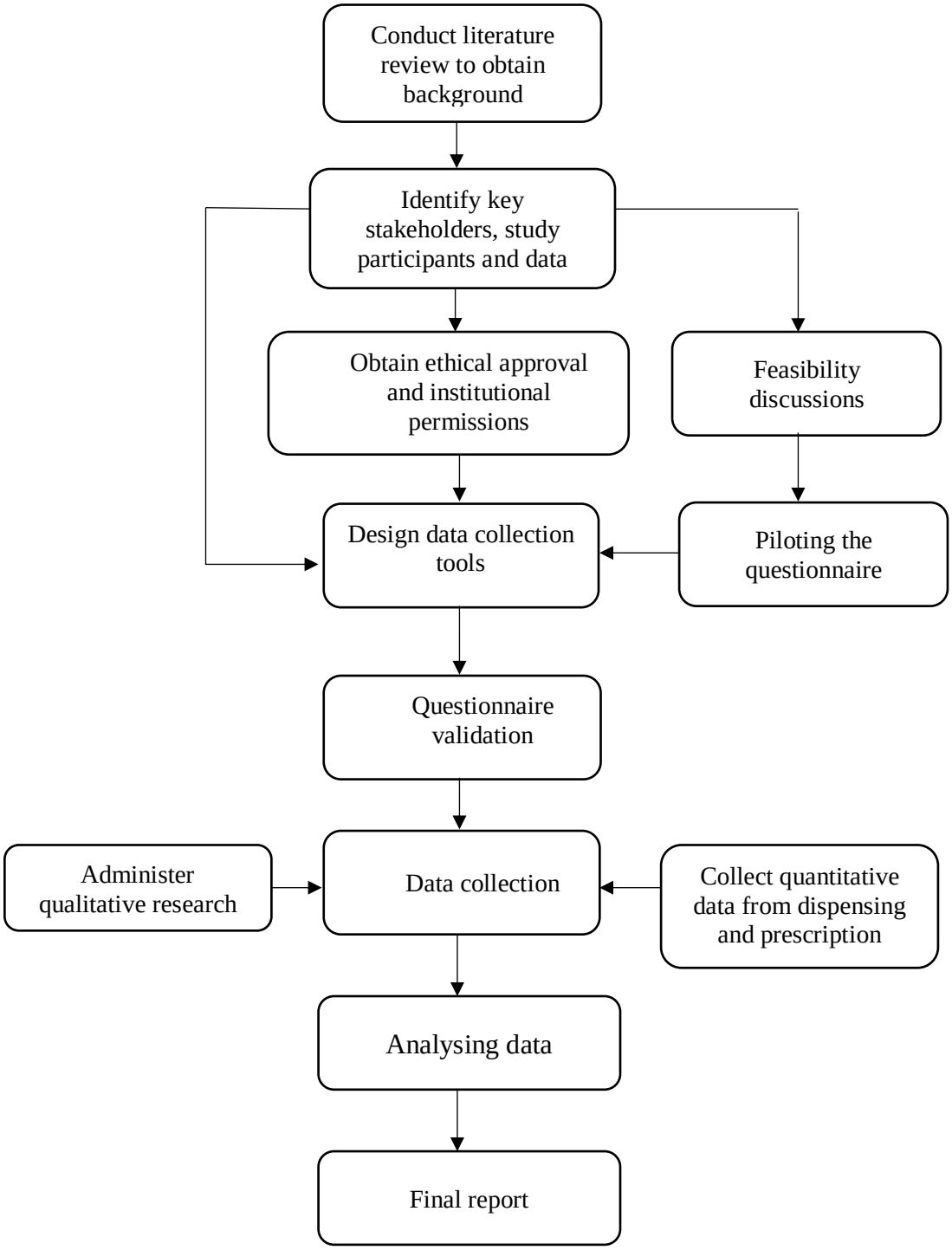

Figure 2.1 Study overview

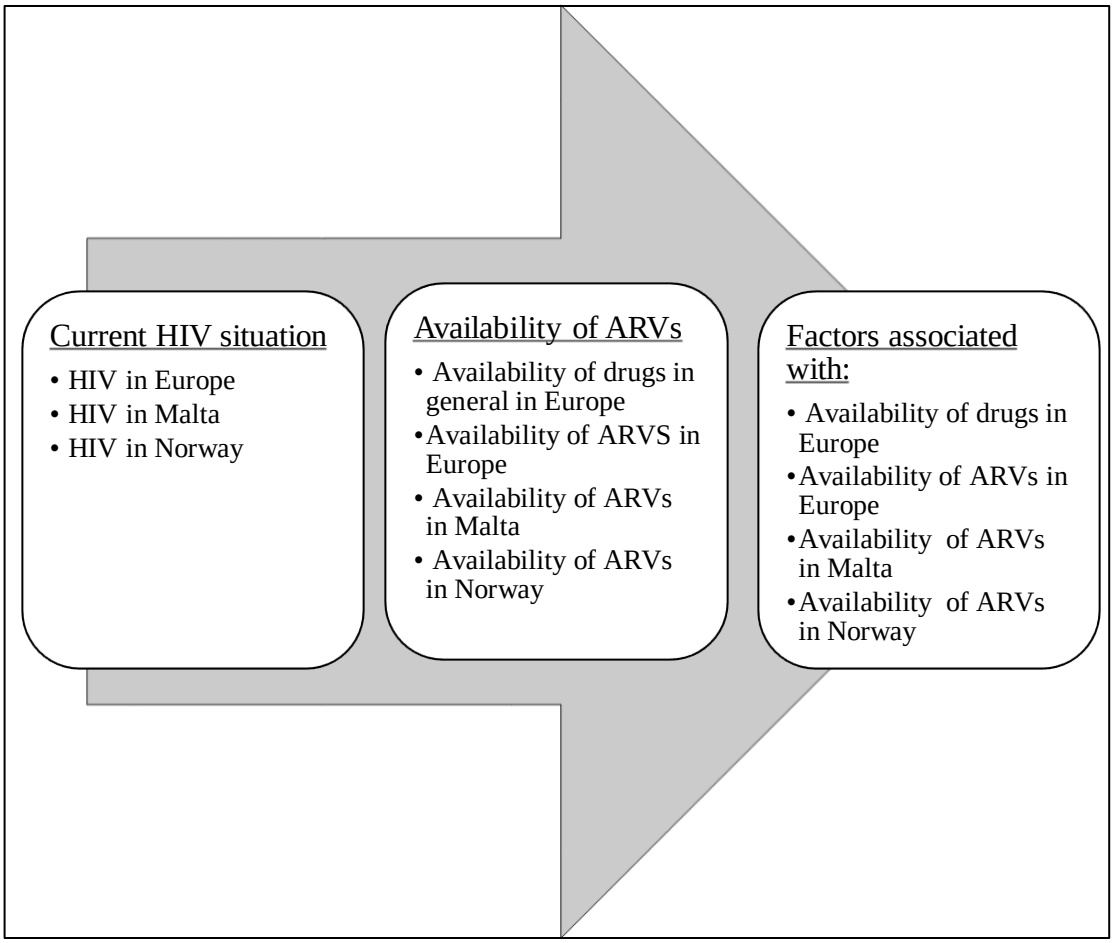

Figure 2.2 Topics included in the literature search

2.4.2 Stakeholders and study participants in Norway

HIV patients in Norway are managed by infectious diseases specialists at hospitals, but dispensing of ARVs is decentralised. Patients obtain ARVs from any community pharmacy of their preference, so data was sourced from community pharmacy dispensing records instead of the general referral hospital as was the case in Malta. Records of all prescription medicines dispensed in Norway are kept in the Norwegian Prescription Database (NorPD), and data from NorPD can be restricted to the desired study setting, in this case, Western Norway. For research purposes the data could be de-identified allowing patient confidentiality to be maintained.

The Norwegian Medicines Agency is involved in the pricing of medicines in Norway and works hand in hand with the national medicines procurement agency, Sykehusinnkjøp. The Norwegian Medicines Agency and Sykehusinnkjøp were identified as stakeholders; employees of these agencies were to be interviewed as key informants.

Electronic mail was sent to the Head of Unit Health Technology Assessment and Reimbursement at the Norwegian Medicines Agency, inviting her to participate in the study and seeking introduction to other stakeholders. Following initial contact, a face to face meeting was set up with the Head of Unit Health Technology Assessment and Reimbursement, and through her a meeting was set up with the Head of Division Sykehusinnkjøp as well, to interview them as key informants in a focused group discussion.

2.5 Development of the key informant interview questionnaire

A questionnaire was designed to collect qualitative data and open-ended questions were used. To design the questionnaire, a literature review was conducted to generate items that cover the scope of drug availability. The generated items (variables) were applied to the context of antiretroviral drugs and formed the elements of the questionnaire. The variables generated are shown in Table 2.1 and the questionnaire is included in Appendix 3 and 4.

A pilot test of the questionnaire was conducted, and the questionnaire was amended based on the results. During the pilot test, the questionnaire was administered to three pharmacists. Based on the responses and comments of the pharmacists, the questionnaire

was modified so that it accurately captures the information it was intended to collect. The questionnaire developed comprises four parts (Part A-D): procurement of antiretroviral drugs, availability of antiretroviral drugs, payment for antiretroviral drugs and availability of PrEP as shown in Table 2.1.

Table 2.1 Variables generated for the study questionnaire on availability of antiretroviral drugs

PART A 1. Procurement practices o Responsible body/bodies o Factors determining what is procured o Participation in pooled procurement schemes o Comparability of antiretroviral prices to international reference prices o Types of pharmaceutical companies from which ARVs are procured – originator vs generic o Presence of locally manufactured ARVs	**PART B** 2. Availability of antiretrovirals o Predominant source of ARVs – originator vs generic o Specific ARVs available o Frequency of shortages o Duration of shortages o Handling of shortages
PART C 3. Payment for antiretroviral drugs o Cost of ARVs to patients	**PART D** 4. Availability of pre-exposure prophylaxis o Presence or absence of PrEP o Cost of PrEP

2.6 Validation of the questionnaire

The questionnaire was validated by a panel of 5 pharmacists using the content validity index (CVI) method as shown in Appendix 5. The CVI method is widely used for determining validity of data collection instruments (Polit et al., 2007). Permission was obtained to use the validation method (Appendix 6). The CVI of the questionnaire was determined by calculating the proportion of total items judged as content valid. All the pharmacists assessed the instrument as valid.

2.7 The dispensing data collection sheet

The tool in Appendix 7 was used to collect dispensing data from Mater Dei Hospital and NorPD. The dispensing data collection sheet comprises of variables necessary to identify ARVs dispensed to patients by ATC code, brand name, and quantity dispensed.

2.8 Inclusion and exclusion criteria for key informant interviews

Inclusion and exclusion was based on information gathered during the initial study feasibility meetings and on the identified key stakeholders. The study participants in both Malta and Norway were pharmacists involved in the procurement, and provision of antiretroviral therapy. All participants had to be fluent in English.

In Norway, this included pharmacists employed in the national health procurement body Sykehusinnkjøp, and the Norwegian Medicines Agency. In Malta, this included pharmacists involved in dispensing of ARVs at Mater Dei Hospital and procuring ARVs at the Central Procurement and Supplies Unit. Physicians and nurses involved in the provision of antiretroviral therapy were not interviewed for data collection.

2.9 Data Collection

Qualitative data was collected using the key informant interview questionnaire (Appendix 3 and 4), and quantitative data was obtained from the prescription and dispensing databases.

2.9.1 Administering the key informant interview questionnaire

Purposive sampling was used in recruiting interview respondents. Purposive sampling is important for the identification and selection of information-rich cases for the most effective use of limited resources (Palinkas et al., 2015). The respondents provided informed consent to participate in the study. The informed consent form in Appendix 7 was used.

The questionnaire (Appendix 4 and 5) was administered through face-to-face in-depth interviews between the researcher and respondent. Face-to-face interviews were used as they presented the best way to obtain in-depth data on the subject matter. During the interviews the respondents were probed further for relevant information if the response to a particular question warranted it. This would not have been possible with a self-administered questionnaire.

Participants were prompted to provide additional information in the further comments section at the end of the questionnaire. This provided an avenue for respondents to provide additional in-depth information relevant to the study questions. The questions were open-ended and in addition to soliciting a response to the question itself, the

interview questions acted as a prompt for the respondent to provide more information related to the question. The questionnaire acted as a guide for an expert discussion, and respondents were not restricted to giving short direct answers. They were encouraged to build up on the answer given, and probed to expand on their response when necessary.

The time allocated for each interview was between 30 minutes and 1 hour. The duration of each interview differed based on the participant's responses. All questionnaires were administered by the principal researcher, which ensured uniformity of interview style.

2.9.2 Collecting dispensing data in Malta

The study tool in Appendix 7 was used to collect data from the dispensing and prescription databases. The dispensing of antiretroviral drugs at Mater Dei Hospital in Malta is computerised, and an electronic record is kept of every dispensing encounter. Data was collected for every ARV dispensing encounter that occurred in the 18 months from January 2016 to June 2017. The data was exported in to a Microsoft Excel sheet for analysis.

2.9.3 Collecting dispensing data in Norway

An online application for data was submitted to the Norwegian Institute of Public Health for data from NorPD. Data was requested for every ARV dispensing encounter that occurred in the 18 months from January 2016 to June 2017. An Excel sheet showing the required variables (Appendix 8) was submitted along with the application, as required by

the Norwegian Institute of Public Health. The requested data was provided in excel sheet format.

2.10 Assessing adherence to antiretroviral therapy

In partnership with the World Health Organisation and Management Sciences for Health, the International Network for Rational Use of Drugs (INRUD) validated a method to assess adherence at health facility level using routine data available at a hospital pharmacy such as dispensing records (Chalker et al., 2009; Ross-Degnan et al., 2010). The method and tools are publicly available for download and use; permission to use them is not required.[23, 24] The INRUD method was used in this study to determine adherence to ARVs by determining how regularly patients attended scheduled pharmacy visits to receive ARV refills.

2.10.1 Definition of study population for determining adherence

To allow for adequate follow-up, the following patients were excluded from all analyses

- Patients with less than 3 visits
- Patients with their first visit less than 180 days before end of follow-up (30 June 2017)
- Patients who only received Truvada or other generic forms of Truvada

[23] Management Sciences for Health. New manual released to help health facilities determine adherence rates to AIDS treatment [Internet]. Management Sciences for Health; 2011 [Cited 2017 Jan 10]. Available from https://www.msh.org/news-events/stories/new-manual-released-to-help-health-facilities-determine-adherence-rates-to-aids

[24] International Network for Rational Use of Drugs. Adherence Survey Tools and Manual [Internet]. INRUD. [Cited 2017 Jan 10]. Available from https://sites.google.com/a/msh.org/inrud-archive/arv-adherence-project/adherence-survey-tools-and-manual

2.10.1.1 Definition of study population in Norway for measuring adherence

The original dataset with prescriptions in Norway contained 38605 prescriptions among 5282 patients. After exclusion of patients who had their first prescription less than 180 days before June 30th 2017, there were 4646 patients left with a total of 37294 prescriptions of which several were on the same date.

In cases where patients had several drugs prescribed on the same day, drugs were sorted by the number of defined daily doses (DDD) per drug and the one with the highest DDD was kept. The drug with the highest DDD was chosen because it determined the latest date on which a refill for the drug combination regimen could be obtained. In cases where two drugs had the same DDD one of them was selected at random. After deletion of repeated prescriptions on the same date, 25 857 prescriptions were left distributed among 4646 patients. Among these patients, 128 received only Truvada or equivalent drugs and all 472 prescriptions for these patients were deleted. Finally, 476 patients with less than 3 visits were deleted, leaving 24 679 visits among 3991 patients.

2.10.1.2 Definition of study population in Malta for measuring adherence

The original dataset with prescriptions in Malta contained 5503 prescriptions among 361 patients. After exclusion of patients who had their first prescription less than 180 days before 30th June 2017 there were 319 patients left with a total of 5335 prescriptions, of which several were on the same date. In cases where patients had several drugs prescribed on the same day, prescriptions were sorted by the number of defined daily doses (DDD) and the one with the highest DDD was kept. The drug with the highest DDD was chosen

because it determined the latest date on which a refill for the drug combination regimen could be obtained. In cases where two drugs had the same DDD one of them was selected at random. After deletion of repeated prescriptions on the same date, 2338 prescriptions were left distributed among 319 patients. Finally, 54 patients with less than 3 visits were deleted, leaving 2267 visits among 265 patients.

2.10.1.3 Adherence measures

Percentage of days covered (PDC) was calculated according to the following formula:

$$\frac{Sum\ of\ DDDs\ prescribed\ during\ follow-up}{(Date\ of\ last\ dispensing - Date\ of\ first\ dispensing) + DDD\ for\ last\ dispensing}$$

For patients with more than 100% coverage, PDC was set to 1.

In addition to the continuous PDC, other categorical variables were made:

- Less than 95% of days covered and 95% or more days covered.
- 0-19%, 20-39%, 40-59%, 60-79% and ≥80% of days covered.

In addition, adherence variables were made indicating if a person had all refills of prescriptions within the scheduled refill date using four different time slots:

- Refill on the scheduled refill date for all prescriptions
- Refill before or within 3 days of the scheduled refill date for all prescriptions
- Refill before or within 30 days of the scheduled refill date for all prescriptions
- Refill before or within 60 days of the scheduled refill date for all prescriptions

The scheduled refill date after the first prescription date was calculated by adding the number of days according to the DDD for the first prescription. If the second prescription

date was early (before the first scheduled refill date), the third scheduled refill date was adjusted by adding the number of DDD for prescription number two to prescription date number two + the number of DDDs left from the previous prescription (Murphy et al., 2012). This adjustment was done for all consecutive prescriptions.

Adherence was evaluated after each prescription and then combined into one adherence measure for all prescriptions combined for each patient. Adherence after the last prescription date was only included if follow-up after the last scheduled refill date was long enough. For example, in evaluation of adherence defined as refill within 30 days after the scheduled refill date, adherence after the last prescription was only considered if the last scheduled refill date was at least 30 days before June 30th.

2.11 Statistical and other analysis

Quantitative data was analysed using SPSS, while qualitative data was analysed using thematic coding.

2.11.1 Analysis of quantitative data

Quantitative data collected from NorPD and Mater Dei dispensing database was fed into a password protected Excel sheet database, and analysed using SPSS version 23.

Adherence was compared between Malta and Norway using Wilcoxon rank-sum test for the continuous PDC-variable because of a highly skewed distribution. For all the categorical variables chi-square tests were used to compare the two countries. The p-value was considered significant if below 0.05.

For all patients, a variable for proportion of visits missed was calculated as number of missed visits divided by (number of visits-1). This variable was analysed using Wilcoxon rank-sum test. For the Norwegian data, logistic regression was used to investigate sex and age as predictors for adherence. The odds ratio was also determined.

2.11.2 Analysis of qualitative data

Qualitative data collected from interview respondents during face-to-face meetings was recorded using a digital voice recorder and saved on a password protected media card. The recordings were transcribed into a Microsoft Word document and the audio files were deleted right after transcribing.

Qualitative data was analysed by thematic analysis (Vaismoradi et al., 2013). Themes were generated from the responses to the interview questions. Data collected was then grouped according to the identified themes.

CHAPTER 3:

RESULTS

Chapter 3: Results

3.1 Quantitative data

Dispensing data was obtained for all patients that received ARVs in Norway and Malta between January 2016 and June 2017.

3.1.1 Baseline characteristics of patients

In Malta 361 patients received ARVs during the study period, and 5282 received ARVs in Norway. Male patients made up 65.5% (n=3991) of the study population in Norway. Dispensing records in Malta did not include patient age or gender.

3.1.2 Antiretroviral drugs available in Malta

Nineteen drugs were available in Malta for the treatment of HIV (Table 3.1). Only multiple pill regimens were dispensed and none of the patients was on a single-tablet regimen. Of the newer ARVs, only raltegravir and darunavir/ritonavir were prescribed. The newer ARVs made up 4.8% and 0.1% (n=5657) of prescriptions respectively. The combination of lamivudine and zidovudine was the most frequently prescribed ARV in Malta 22.9% (n=1297), closely followed by lopinavir/ritonavir 21.5% (n=1216) (figure 3.1).

Table 3.1 Prescription of antiretroviral drugs in Malta between January 2016 and June 2017 (N=5657)

Antiretroviral drug	Number of prescriptions	Percentage
Lamivudine 150mg / Zidovudine 300mg	1297	22.9%
Lopinavir 200mg / Ritonavir 50mg Tablets	1216	21.5%
Tenofovir 245mg	950	16.8%
Lamivudine 150mg tablets	741	13.1%
Efavirenz 600mg	676	11.9%
Raltegravir 400mg tablets	263	4.6%
Nevirapine 200mg	131	2.3%
Abacavir 600mg + Lamivudine 300mg tablets	119	2.1%
Zidovudine 100mg capsules	57	1.0%
Didanosine 125mg tablets	24	0.4%
Lamivudine Syrup	22	0.4%
Abacavir 300mg	18	0.3%
Lopinavir 100mg /Ritonavir 25mg (Paediatric)	17	0.3%
Lamivudine 100mg	15	0.3%
Maraviroc 300mg tablets	15	0.3%
Raltegravir 100mg oral granules	12	0.2%
Zidovudine 10mg/ml syrup	11	0.2%
Darunavir 600mg	6	0.1%
Ritonavir 100mg capsules	6	0.1%

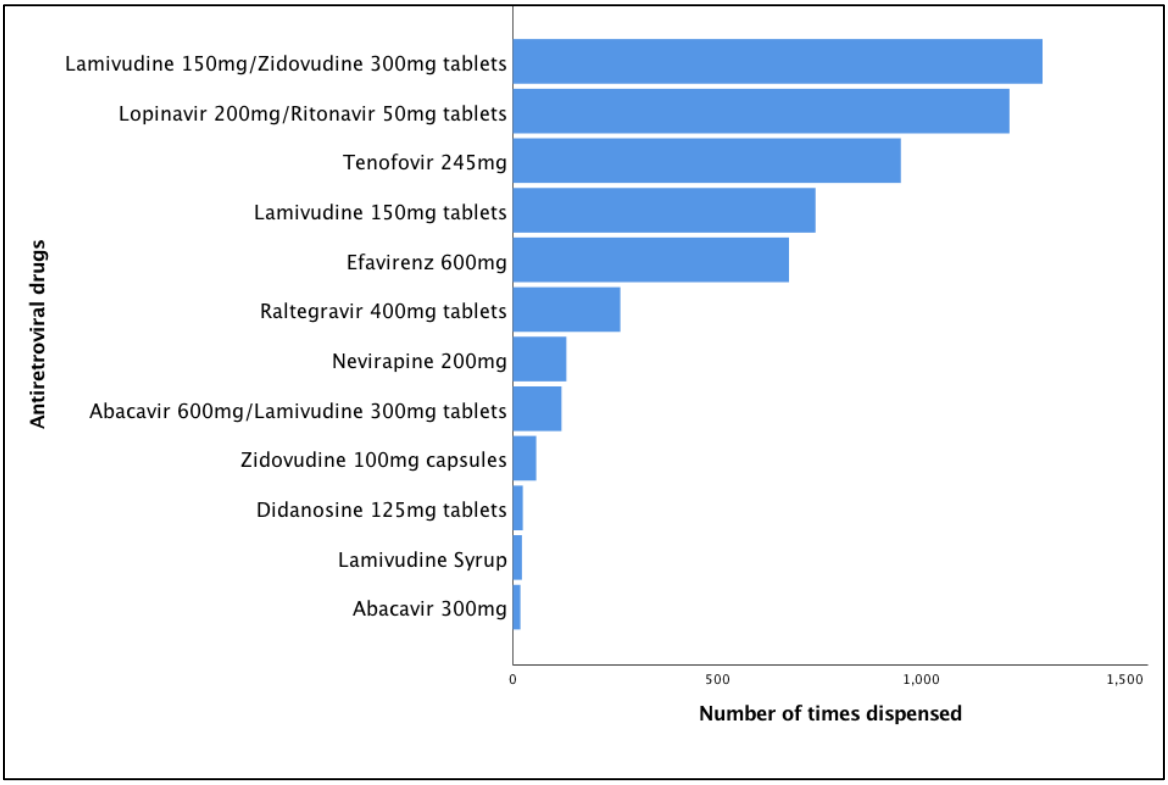

Figure 3.1 Most frequently prescribed antiretroviral drugs in Malta (N=12)

3.1.3 Antiretroviral drugs available in Norway

Up to 44 drugs were dispensed to patients between January 2016 and June 2017 (Table 3.3). Single-tablet regimens made up 32.8% (N=38605) of ARVs dispensed and 23.4% were for newer ARVs. Figure 3.2 shows the most frequently prescribed ARVs in Norway.

Table 3.2a) Prescription of antiretroviral drugs in Norway between January 2016 and June 2017 (N=5942)

Trade name + formulation dose	Active ingredient	Freq*	%
Truvada tab	*emtricitabine/tenofovir disoproxil fumarate*[1]	*5942*	*15.4*
Triumeq tab 50/600/300mg	abacavir, dolutegravir, and lamivudine	5151	13.3
Atripla tab	efavirenz/emtricitabine/tenofovir disoproxil fumarate	2981	7.7
Norvir tab 100mg	Ritonavir	2848	7.4
Tenofovir disoproxil tab 245	*Tenofovir disoproxil*	*2711*	*7.0*
Genvoya tab 150/150/200/10mg	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	2576	6.7
Eviplera tab 200/25/245mg	emtricitabine, rilpivirine and tenofovir disoproxil	2498	6.5
Isentress tab 400mg	Raltegravir	2070	5.4
Reyataz orifarm kaps 300mg	Atazanavir	1254	3.2
Tivicay tab 50mg	Dolutegravir	1047	2.7
Stribild tab 150/150/200/245mg	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	988	2.6
Odefsey tab 200/25/25mg	emtricitabine, rilpivirine, & tenofovir alafenamide	955	2.5
Kivexa tab	*Abacavir/lamivudine*	*828*	*2.1*
Prezista tab 800mg	Darunavir	745	1.9
Reyataz kaps 200mg	Atazanavir	708	1.8
Reyataz kaps 300mg	Atazanavir	677	1.8
Kaletra tab 200/50mg	Lopinavir/ritonavir	584	1.5
Viramune depottab 400mg	Nevirapine prolonged-release tablets	584	1.5
Descovy tab 200/25mg	emtricitabine and tenofovir alafenamide	407	1.1
Combivir tab	*lamivudine and zidovudine*	*344*	*0.9*
Ziagen tab 300mg	Abacavir	344	0.9
Rezolsta tab 800/150mg	darunavir and cobicistat	278	0.7
Prezista tab 600mg	Darunavir	259	0.7
Efavirenz sandoz tab 600mg	*Efavirenz*	*196*	*0.5*

***** - Frequency – number of prescriptions

Table 3.2b) Prescription of antiretroviral drugs in Norway between January 2016 and June 2017 (N=5942)

Trade name + formulation dose	Active ingredient	Freq*	%
Descovy tab 200/10mg	emtricitabine and tenofovir alafenamide	167	0.4
Stocrin orifarm tab 600mg	*Efavirenz*	*156*	*0.4*
Epivir tab 150mg	Lamivudine	146	0.4
Intelence tab 200mg	Etravirine	145	0.4
Epivir tab 300mg	Lamivudine	113	0.3
Edurant tab 25mg	Rilpivirine	100	0.3
Epivir mikst 10mg/ml	Lamivudine syrup	81	0.2
Combivir orifarm tab	*lamivudine and zidovudine*	*80*	*0.2*
Ziagen mikst 20mg/ml	Abacavir syrup	62	0.2
Zidovudine tab 300mg	Zidovudine	60	0.2
Vemlidy tab 25mg	tenofovir alafenamide fumarate	55	0.1
Abacavir/Lamiv myl tab 600/300	*Abacavir/Lamivudine*	*43*	*0.1*
Isentress tyggetab 100mg	Raltegravir	35	0.1
Stocrin tab 200mg	Efavirenz	35	0.1
Trizivir tab	Abacavir/lamivudine/zidovudine	33	0.1
Kaletra mikst 80+20mg/ml	Lopinavir/ritonavir syrup	29	0.1
Celsentri tab 150mg	Maraviroc	26	0.1
Evotaz tab 300/150mg	Atazanavir/cobicistat	25	0.1
Emtriva kaps 200mg	Emtricitabine	24	0.1
Reyataz kaps 150mg	Atazanavir	23	0.1
Invirase tab 500mg	Saquinavir	17	0.0
Celsentri tab 300mg	Maraviroc	14	0.0
Stocrin tab 50mg	Efavirenz	12	0.0
Emtricitabin/tenof san 200/245	*Emtricitabine/tenofovir disoproxil*	*11*	*0.0*
Kaletra tab 100/25mg	Lopinavir/ritonavir	10	0.0
Retrovir mikst 10mg/ml	Zidovudine syrup	6	0.0
Viramune tab 200mg	Nevirapine	6	0.0
Viread 2care4 tab 245mg	tenofovir disoproxil	5	0.0
Stocrin tab 600mg	*Efavirenz*	*2*	*0.0*

***** - Frequency – number of prescriptions
[1,2,3,4,5] – Multiple brands of the same active ingredient

Truvada (emtricitabine/tenofovir disoproxil fumarate) was the most frequently prescribed ARV in Norway 15.4% (n=5942), closed followed by Triumeq (abacavir, dolutegravir, and lamivudine) 13.3% (n=5151).

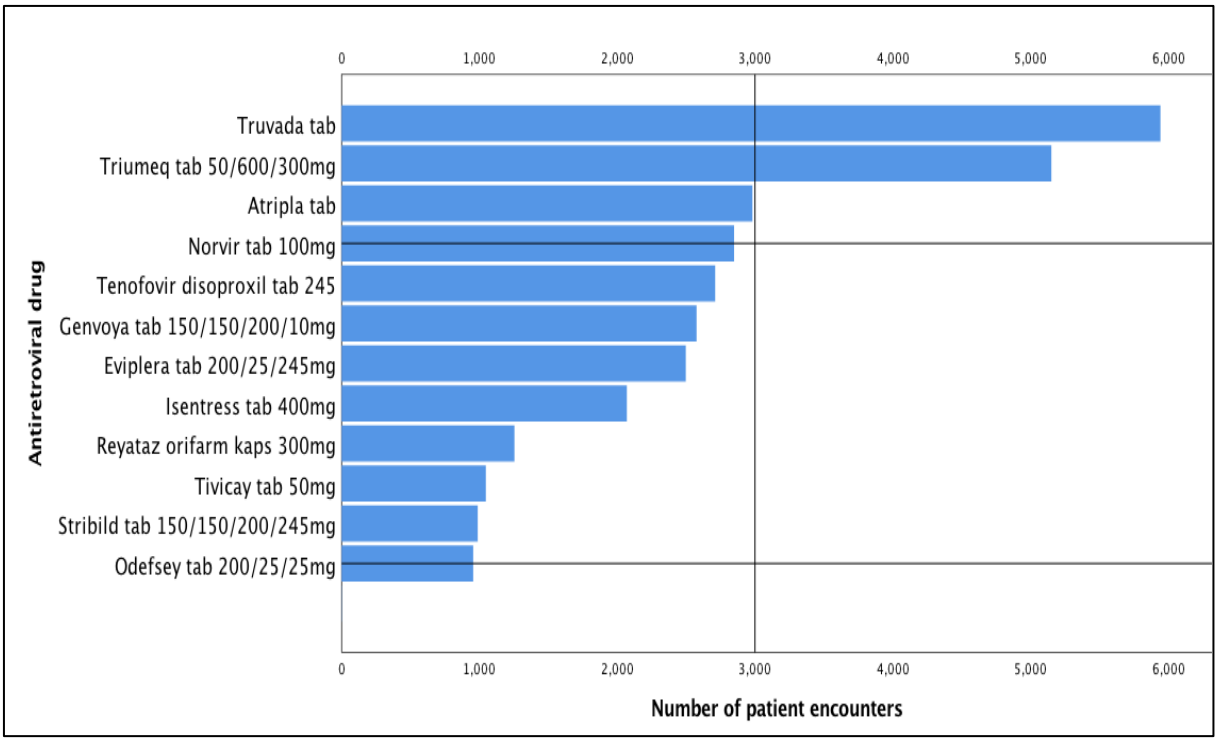

Figure 3.2 Most frequently prescribed antiretroviral drugs in Norway (N=12)

3.1.4 Adherence to antiretroviral drugs

Adherence was defined as patient attendance of pharmacy visits for ARV refills on the expected visit date. The average number of visits per patient in Malta was 8.6 (range 7-10), while that in Norway was 6.2 (range 5-7). Patients in Malta were required to visit the pharmacy for ARV refills every 60 days, while patients in Norway had to obtain refills every 90 days.

Table 3.3 Attendance of pharmacy visits for ARV refills within the scheduled visit days

	Norway (N=3991)	**Malta (N=265)**	**p-value***
Number of visits per person, median (IQR)[a]	6 (5-7) [b]	9 (7-10)[c]	<0.001
All visits on scheduled visit day, n (%)	1053 (26.4)	62 (23.4)	0.28
All visits within 3 days of scheduled visit day, n (%)	1376 (34.5)	103 (38.9)	0.15
All visits within 30 days of scheduled visit day, n (%)	2777 (69.6)	199 (75.1)	0.06
All visits within 60 days of scheduled visit day, n (%)	3006 (82.8)	217 (81.9)	0.69

[a] Refers to number of pharmacy visits for ARV refills during the 18 months of study follow-up
[b] Patients in Norway had to visit the pharmacy for refills every 90 days
[c] Patients in Malta had to visit the pharmacy for refills every 60 days
* P-value from Wilcoxon rank-sum test for number of visits and chi-square test for all other variables

One third of all scheduled patient pharmacy visits in Malta and Norway were missed. There was no significant difference between the proportion of missed visits in Malta and Norway when considering patients who obtained refills on the expected refill date, but there was a significant difference in the proportion of missed pharmacy visits when considering patients who obtained refills with in 3 days from the expected refill date. A third of patients in Norway (N=3991) did not attend a scheduled pharmacy visit with in

3 days of the expected date, compared to 24% (N=265) in Malta. However, by the 30th day from the expected pharmacy visit, an almost equal proportion of patients in Malta and Norway had attended the scheduled pharmacy visit (Table 3.4).

Table 3.4 Proportion of pharmacy visits missed [a]

	Norway [b] (N=3991)	**Malta [c] (N=265)**	**p-value***
Scheduled visit date as time limit			
Proportion of visits missed, mean (SD)	0.37 (0.33)	0.35 (0.31)	0.34
Within 3 days of scheduled visit date as time limit			
Proportion of visits missed, mean (SD)	0.31 (0.32)	0.24 (0.29)	0.001
Within 30 days of scheduled visit date as time limit			
Proportion of visits missed, mean (SD)	0.07 (0.18)	0.06 (0.15)	0.93

[a] Refers to the proportion of pharmacy visits for ARV refills that were missed during the 18 months of study follow-up
[b] Patients in Norway had to visit the pharmacy for refills every 90 days
[c] Patients in Malta had to visit the pharmacy for refills every 60 days
* P-value from Wilcoxon rank-sum test

Patients in Malta and Norway had comparable levels of adherence. Both countries had a similar proportion of patients with PDC greater than or equal to 0.95; 71.3% (N=3991) in Norway and 74% (N=265) in Malta. The difference was not statistically significant, (p>0.05). Only half of all patients in Malta and Norway had all medication days covered (PDC = 1), at 52.9% (N=3991) in Norway and 52.5% (N=265) in Malta (Table 3.5).

Table 3.5 Comparison of proportion of days covered (PDC)[1] by ARV refills between Norway and Malta

	Norway (N=3991)	**Malta (N=265)**	**p-value***
PDC, mean (SD)	0.94 (0.12)	0.94 (0.12)	
PDC, median (IQR)	1 (0.93-1)	1 (0.95-1)	0.80
Categories of PDC, n (%)			
<0.20	1 (0.03)	0 (0)	
0.20-0.39	29 (0.7)	0 (0)	
0.40-0.59	72 (1.8)	10 (3.8)	
0.60-0.79	342 (8.6)	23 (8.7)	
≥ 0.80	3547 (88.9)	232 (87.6)	0.15
PDC ≥ 0.95	2847 (71.3)	196 (74.0)	0.36
PDC=1	2112 (52.9)	139 (52.5)	0.88

* p-value from Wilcoxon rank sum test for continuous PDC and chi-square test for categorizations of PDC
[1] Proportion of days covered (PDC) measures the percentage of days in a dispensing time interval that are covered by the ARVs dispensed.
SD – Standard deviation
IQR – Interquartile range

Among Norwegian patients, the age distribution between men and women differs. Among women, 66% are born 1970 or later while the corresponding percentage among men is 45.6% (Table 3.6).

Table 3.6: Association between sex and age among Norwegian patients (n=3986)

Birth year	**Female (N=1377)**	**Male (N=2609)**	**P-value***
1949 or earlier, n (%)	24 (1.7)	189 (7.2)	<0.001
1950-1969, n (%)	445 (32.3)	1232 (47.2)	
1970-1989, n (%)	853 (62.0)	1097 (42.1)	
1990-2010, n (%)	55 (4.0)	91 (3.5)	

*P-value from chi-square test

Since there is an association between age and adherence, the odds ration (OR) for sex is reduced after adjustment for age (Table 3.7). When birth year is used as a continuous variable the OR is 0.95 which means that a one-year increase in age is associated with 5% reduced odds of being adherent. Older age is associated with better adherence.

Table 3.7 Age and sex as predictors of pharmacy visit attendance within 30 days of the scheduled visit date in Norway

			Unadjusted		**Mutually adjusted***	
	Number of patients	**All visits within 30 days of scheduled visit date, n (%)**	**Odds Ratio (OR) (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Sex						
Female	1380	926 (67.1)	1		1	
Male	2611	1851 (70.9)	1.19 (1.04-1.37)	0.01	1.15 (1.00-1.33)	0.05
Birth year in categories						
1990-2010	146	91 (62.3)	1		1	
1970-1989	1950	1312 (67.3)	1.24 (0.88-1.76)	0.22	1.25 (0.88-1.77)	
1950-1969	1677	1215 (72.5)	1.59 (1.12-2.26)	0.01	1.57 (1.10-2.23)	
1949 or earlier	213	157 (73.7)	1.69 (1.08-2.67)	0.02	1.64 (1.03-2.58)	
Birth year as continuous variable	3986	2775 (69.6)	0.95 (0.92-0.98)	<0.001	0.95 (0.92-0.98)	0.001

* OR for sex is adjusted for birth year and OR for birth year is adjusted for sex.

Adherence was high among patients that had at least 3 visits within the first 3 months of observation. There were 2070 patients in Norway that had 3 visits within their first 180 days of follow-up, and 239 patients in Malta that had 3 visits within their first 180 days of follow-up. Ninety percent (N=2070) of such patients in Norway and 83% (N=239) of such patients in Malta had a high adherence at a PDC ≥ 95.0%. Among these patients, 86% (N=2070) in Norway had all 180 days of medicine covered by the obtained ARV refills (PDC=1) while 60% (N=239) in Malta had all 180 days of medicine covered by their ARV refills (Table 3.8).

Table 3.8 Comparison of proportion of days covered (PDC)[1] between Norway and Malta when restricting to first 180 days of follow-up and at least 3 visits

	Norway (N=2070)	**Malta (N=239)**	**p-value***
Number of visits per person, median (IQR)	3 (3-4)	4 (3-4)	
PDC, mean (SD)	0.98 (0.06)	0.97 (0.05)	
PDC, median (IQR)	1 (1-1)	1 (0.97-1)	<0.001
Categories of PDC, n (%)			
<0.20	0	0	
0.20-0.39	1 (0.05)	0	
0.40-0.59	13 (0.6)	0	
0.60-0.79	42 (2.0)	4 (1.7)	
≥ 0.80	2014 (97.3)	235 (98.3)	0.69
PDC ≥ 0.95	1876 (90.6)	198 (82.6)	<0.001
PDC=1	1781 (86.0)	143 (59.8)	<0.001

[1]Proportion of days covered (PDC) measures the percentage of days in a dispensing time interval that are covered by the ARVs dispensed.

3.2 Qualitative data

Several factors were identified from key-informant interviews as affecting the availability of ARVs in Malta and Norway.

3.2.1 HIV treatment policy and cost of ARVs to patients

In both Malta and Norway, ARVs were provided free of charge by, the national health services, to patients diagnosed with HIV. Foreign nationals, EU/EEA citizens in particular, were also able to receive treatment on presentation of the required entitlement documentation from their countries. Patients not eligible for free medications, that is patients that are not covered under the national health insurance scheme, are required to pay.

3.2.2 Procurement in Malta

The Central Procurement & Supplies Unit (CPSU) is the body responsible for procuring ARVs in Malta. Both generic and originator brand ARVs were approved for use in Malta. Malta did not have locally manufactured ARVs, and was not part of any joint/pooled procurement schemes for ARVs with other countries. Factors considered when procuring ARVs in Malta included quantity, resistance and cost. Conventional (older) ARVs were procured using standard procurement guidelines of the drug management cycle, that is use-selection-procurement-distribution, similar to other pharmaceuticals on the Mater Dei Hospital formulary.

3.2.2.1 Formulary and forecasting challenges

Newer ARVs were not part of the hospital formulary, and could only be obtained through a special requisition system, called the exceptional medicinal treatment route (also known as named patient basis). This requisition system was performed on a case by case basis as needed for each patient that was prescribed a newer ARV. As a result, forecasting of quantities for newer ARVs could not be performed satisfactorily.

"*And another thing is, currently there is a system in hospital: the exceptional medicinal treatment route, where patients that are approved on exceptional basis and HIV has been approved for, can obtain some new drugs through this system. But it's (HIV) not exceptional any longer. So, costs are increasing. And the problematic issue with this is that when you issue a bid the P.A will tell us, "approved for 1 patient." But in the long run when I lookback throughout the year, I would see that 12 patients were approved. So, if I would have issued the right forecast, I would have got a better price rather than having one patient."* – Key-informant interview, Mater Dei Hospital, Malta.

Some pharmaceutical companies were not willing to continue supplying Mater Dei Hospital with some drugs such as zidovudine, citing the absence of an upright forecast from the hospital and the fact that the company has newer drugs than zidovudine.

"The exceptional medicinal treatment route is used for some HIV drugs which are no longer exceptional. For example, raltegravir one of the new ones, but using this as a loophole because it's not included in the formulary. And we still procure. But we are procuring at a higher expense also, you know when you don't join volumes. Also, we need

to involve - if it's an emergency - a courier, traveling. If we have volumes together, we need to work smarter." – Key-informant interview, Mater Dei Hospital, Malta.

3.2.2.2 Price reduction strategies in Malta

To select suppliers for ARVs, tenders for bids were published, and the cheapest technical compliant bidder selected as the supplier. Price reduction strategies employed in procuring ARVs included capping prices, increasing volume of orders – to benefit from the favourable price per volume, and the "package deal." The package deal mechanism is one in which CPSU procures from pharmaceutical companies not just the medication, but the complimentary monitoring tools such as software and other materials such as laboratory supplies that assist clinicians in monitoring therapy and resistance patterns. CPSU believed that this "package deal system" would increase the volume of orders on ARVs and lower costs.

"However since, you know, funding is important and funding is not always available, for Hepatitis for example, CPSU came up with an innovative way of procurement. We didn't go through the normal route. We did good market research. Like for example seeing what's available around the globe, what therapeutic guidelines should be followed internally - we sat down with the clinician team - and came up with a request for participation, which is a procurement cycle, for curative treatment for Hepatitis C; which includes the medicine, the monitoring, adherence, and the actual therapy … HIV will follow suit." – Key-informant interview, Mater Dei Hospital, Malta.

Cost and the constantly evolving nature of HIV treatment were important factors in procuring ARVs in Malta.

"In procurement, no one size fits all. Even though there are procurement books, for Malta we need to take things differently. Both because of its geographical position and its size. Though Malta is small, in the case of HIV we have a high risk of HIV and also a high number of patients on HIV. So, obviously, the procurement strategy is as such that usually we use standards like for example to procure especially a generic medicine just as for other drugs. The problem with HIV as I was telling you is that they become old or maybe they become resistant toward the patient."

"With respect to HIV, again there's no allocated funds like (for) oncology. So, we also need to think outside the box." – Key-informant interview, Mater Dei Hospital, Malta.

3.2.2.3 Political will

Political will influenced priorities in health care spending.

"And the Advisory Health Care Benefits, which is a multi-team, it considers the financial consideration. And, like, what should be priority for the department. What is the political priority in the department? For example, in the last year and a half, oncology was a priority for the department. With regards to infectious diseases, Hepatitis C took over HIV. So, we did invest in Hep C. Probably in 5 years' time if everything goes well, Malta will be one of the first countries who will have eliminated Hep C from the local island." – Key informant interview, Mater Dei Hospital, Malta.

3.2.2.4 Procurement in Norway

Findings showed that procurement of ARVs in Norway was decentralised. While health technology assessments, price capping and negotiation were centralised and under the mandate of the national insurance scheme and national health procurement body Sykehusinnkjøp, ARVs were procured and distributed by wholesalers and community pharmacies.

3.2.2.5 Formulary and forecasting challenges

Clinicians in Norway were able to prescribe any ARV without being limited by the absence of the drug on the formulary. According to Norwegian legislation, for conditions approved for reimbursement under the national insurance scheme (NIS), all drugs used in managing the said condition are reimbursable. HIV/AIDS being one of those conditions, all ARVs including newer ARVs did not require special application to be procured.

"In Norway, we have a law that for severe infectious diseases, medicines are free. And it is free also for patients that come into Norway, just visitors. And we have a list of these diseases that are on that list to be financed. And that's called the Paragraph 4 list … The consequences of that is if the disease (not the pharmaceutical but the disease) is on that list, that means that all the drugs that have the ATC code J01 is to be fully reimbursed."- Key informant interview, Norway.

3.2.2.6 Price reduction strategies in Norway

Findings showed that Norway uses reference pricing using 9 predefined countries in Northern Europe as the reference countries, as well as price capping and negotiation to obtain a favourable price for ARVs. The Norwegian Medicines Agency (NOMA) played a central role in determining prices for drugs procured in Norway, alongside the national procurement body, Sykehusinnkjøp. NOMA conducted the reference pricing, health technology assessments, and set the maximum prices for prescription medicines, while Sykehusinnkjøp conducts the negotiations with pharmaceutical companies. The willingness to pay for ARVS was reported to be high.

"And then you come in to the willingness to pay. Where is the willingness to pay? Is there a fixed threshold? How much are we willing to pay? And in Norway there is not a fixed threshold but our politicians have said that the more severe a disease is and the more gain you get from a treatment, the willingness to pay is higher. But of course, there is a limit." – Key informant interview, Norway.

" The willingness to pay is 100% on Paragraph 4(conditions)." – Key informant 2 – Norway.

While no challenges were reported in sourcing newer ARVs in Norway, and a high willingness-to-pay was reported, findings from key-informant interviews showed that the small market size and current procuring model raised the cost of ARVs. As a result, the procurement body was in the process of implementing a new system of sourcing ARVs that involved tenders and bidding in order to potentially lower the cost of ARVs. This

mandate was being shifted from the national insurance scheme (centralised) to the regional hospital trusts (decentralised).

"As of today, drugs for infectious diseases are financed in the NIS. From 2018, financing will be moved to the hospitals, but for the patient it will make no difference (because the medicine will still be free)."- Key informant interview, Norway.

Norway did not participate in any joint/pooled procurement schemes for ARVs.

3.2.2.7 Political will

Political will in Norway was actively in favour of enhancing HIV care. Legislation in Norway supported use of all necessary ARVs, and politicians favoured the high willingness to pay for pharmaceuticals for serious infectious diseases.

"… in Norway there is not a fixed threshold but our politicians have said that the more severe a disease is and the more gain you get from a treatment, the willingness to pay is higher..." – Key informant interview, Norway.

3.2.3 Pre-exposure prophylaxis (PrEP)

PrEP was provided free of charge in Norway, but not provided in Malta. Pharmacists interviewed in Norway reported observing an increase in prescriptions for Truvada (emtricitabine+tenofovir disoproxil fumarate), a regimen used for PrEP. Interview respondents in Malta all reported that PrEP was not provided in Malta.

3.3 Published Work

A poster presentation of this study (Appendix 10) was presented at the Global Health Conference held at the University on Oslo from 10th to 11th April 2018.

CHAPTER 4

DISCUSSION

Chapter 4: Discussion

4.1 Centralisation and decentralisation of HIV treatment

In Malta, provision of HIV treatment was centralised. All patients received treatment from the national acute general hospital, Mater Dei Hospital. HIV patients in Malta visited the specialist and obtained ARV refills every 60 days. The centralised system of HIV care in Malta in which all patients receive treatment for HIV at Mater Dei Hospital is comparable to some other small European countries such as Croatia. According to the ECDC, all HIV patients in Croatia were treated at the HIV/AIDS centre at the University Hospital for Infectious Diseases in Zagreb. The same survey reports that Finland, the Netherlands, Austria, Bulgaria, Latvia, Serbia among others, have decentralised HIV care. Most of the countries favoured decentralising HIV care to improve access.[25]

In low and middle income countries, decentralisation of HIV management was expanded in efforts to improve access and adherence to treatment, as advocated by the WHO (Scanlon and Vreeman, 2013). Centralisation of HIV treatment in these countries was usually due to resource constraints involved in HIV treatment and monitoring, for example the cost implications and additional human resource required in setting up and scaling up multiple laboratories for CD4 and viral load monitoring (Pham et al., 2017).

[25] European Centre for Disease Prevention and Control. Thematic report: HIV treatment, care and support. Monitoring implantation of the Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia: 2012 progress report [Internet]. Stockholm: ECDC; 2013 [Cited 2017 Sept 19]. Available from https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/dublin-declaration-treatment-care-support.pdf

In Malta, one of the primary reasons for centralisation of HIV care was to maintain confidentiality and privacy of HIV patients and prevent HIV-related stigma. Malta being a small island with a low population, extra measures are taken to ensure that the identity of HIV patients is protected. While centralisation of HIV care in Malta can be justified by the relatively smaller number of HIV patients (361 patients at the time of this researcher's study), findings from the key-informant interviews revealed concerns about the absence of an alternative source of ARVs for patients in the event of failure in the central supply system. The cost implications of decentralising HIV care appeared to be secondary to the need to preserve patient anonymity at all costs.

Provision of ARVs in Norway was decentralised, with patients receiving ARVs from community pharmacies of their preference. WHO recommends integration of ART into primary health care.[26] Norway's approach of decentralised HIV care reflects an integrated system of HIV management. HIV patients attend their GP for regular ART prescriptions, and are referred to an HIV specialist when needed. Norway is geographically larger (323 808 km^2) than Malta (316 km^2); and while Norway has a similar proportion of HIV patients as Malta (5282 patients, 0.1% of the population), it makes financial sense to decentralise HIV care and it increases access to HIV treatment.

Provision of health services in Norway is administered through 4 regional authorities - Northern Norway Regional Health Authority, Midland Regional Health Authority, Joint Southern and Eastern Norway Regional Health Authority, and Western Norway Regional

[26] World Health Organisation. Integrated guidelines for ART in the context of primary health care [Internet]. [Cited on 2018 Mar12] Available from http://www.who.int/hiv/topics/capacity/modules_intro/en/ WHO

Health; and has several regional/referral hospitals.[27] In this context, decentralised HIV care is the best approach.

4.2 Availability of antiretroviral drugs

Antiretroviral drugs (ARVs) were provided free of charge in both Malta and Norway under the national health insurance schemes. This is in line with the HIV treatment policies of other Western European countries, where ART is free for all diagnosed (Nakagawa et al., 2014). Foreign nationals in Malta and Norway were also able to receive treatment on presentation of the required entitlement documentation from their countries.

Both generic and originator brand ARVs were distributed in Malta and Norway. Originator brands were more predominant in Norway but the dispensing data in Malta recorded only the international non-proprietary name (INN) of the drug, so it was not possible to determine the proportion of originator brand ARVs. Single tablet regimens (STRs) were not used in Malta. Generic ARVs currently marketed do not include STRs (Rwagitinywa et al., 2018); but generic ARV use has been shown to reduce treatment costs. A cohort study conducted at a French university hospital clinic found savings of €36 100 to €1472 600/year when ART was switched to generic-based regimens (Papot et al., 2017).

[27] Norwegian Directorate of Health. Norway and Health: an introduction [Internet]. Norwegian Directorate of Health: Oslo; 2012 [Cited 2017 Apr 11]. Available from https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/302/Norway-and-health-an-introduction-IS-1730E.pdf

4.3 Use of newer antiretroviral drugs

Even though many ARVs have comparable efficacy, they vary in terms of frequency of dosing, drug interactions, adverse effects and pill burden (Patel et al., 2014). They also differ in terms of speed of achieving viral load suppression, and newer ARVS have been shown to be more tolerable and achieve faster viral load suppression (McCoy et al., 2018).

This study found that newer ARVs were not widely used in Malta, with only 4.9% (N=5657) of prescriptions accounting for newer ARVs (Table 3.2). Single-tablet regimens were not in use in Malta. These findings confirmed the reports of limited availability of newer ARVs in Malta, and were supported by data obtained through key-informant interviews citing an out-dated formulary as a challenge to availing newer ARVs to all patients on ART.

Since newer ARVs are not part of the Mater Dei Hospital Formulary, all patients that received newer ARVs in Malta obtained them through the exceptional medicinal treatment route, commonly referred to as "named patient basis" in Malta. The exceptional medicinal treatment route allows clinicians to request funding for treatment that is not included in the National Health Service, for specific patients under exceptional circumstances.[28] It is possible that the prescription for newer ARVs in Malta were for patients in whom treatment failure on older ARV regimens was observed. There is evidence to show that when a limited number of ARVs is available, first line agents may

[28] Government of Malta. Ministry of Health. Exceptional Medicinal Treatment (EMT) Request Form. Health Policy [Internet]. Malta: Ministry of Health. [Cited 2018 May 15]. Available from https://servizz.gov.mt/en/Pages/Health-and-Community-Care/Health/Health-Policy/WEB013/default.aspx

be restricted to second line use, to preserve the options available to prescribers and patients in case of treatment failure (Toverud et al., 2012).

In comparison, newer ARVs were more widely used in Norway, including single tablet regimens (STRs). Newer ARVs comprised 23.4% (N=38605) of all ARV prescriptions in Norway and STRs comprised 32.8%. While no challenges were reported in sourcing newer ARVs in Norway, possibly due to the health system's high willingness-to-pay that was reported by interview respondents, findings from key-informant interviews showed that the small market size and current procuring model raised the cost of procuring ARVs in Norway. As a result, the procurement body was in the process of putting in place a new system of sourcing ARVs that involved tenders and bidding in order to potentially lower the cost of ARVs. This new system was to take effect in January 2018. The old system involved negotiating with approved pharmaceutical companies while the new system will involve tenders and bidding.

The higher availability of, and greater volume of prescriptions for, the newer more expensive ARVs in Norway compared to Malta could be attributed to cost, since Norway spends more money on ART than Malta. Malta spends €4.5 per capita and 2.8% (€1.8 million) of the national pharmaceutical expenditure on ART, while Norway spends €12.26 per capita and 5.2% (€61,316,302) of the national pharmaceutical expenditure on ART.

Availability of a wider selection of ARVs affords clinicians and patients the opportunity to individualise treatment. This is possible to a greater extent in Norway, where this study found that 23.4% of ARV prescriptions were of newer ARVs and 44 drugs were used in

managing HIV during the study period, compared to 4.9% and 19 respectively in Malta. This is in line with the findings of a comparison of HIV treatment in Norway to South Africa, which reported that Norway had a larger number of ARVs in use than South Africa, and that individualisation of ART was possible in Norway because of the numerous options available to choose from for an ARV regimen, allowing for optimisation of treatment (Toverud et al., 2012).

Optimising ART prolongs the durability of HIV therapy, especially in highly treatment-experienced patients as these tend to be the ones more prone to development of resistance. Durability of HIV therapy refers to the length of time that a patient is able to achieve effective treatment on a particular regimen before requiring switching to an alternative regimen as a result of treatment failure, adverse effects, or resistance (Sheth et al., 2016). WHO guidelines recommend using newer ARVs and optimising regimens to achieve sustained durability of ART.[29] The initial choice of ARV regimen is important for long-term management of HIV since changing from one regimen to another is associated with increased costs of treatment and greater risk of treatment failure (Fong et al., 2013).

The 2016 WHO guidelines on the use of ARVs include dolutegravir and efavirenz 400mg as new alternative options in first-line ART regimens and are better tolerated than efavirenz at standard 600mg doses. Patients in both Malta and Norway were however still receiving regimens comprising efavirenz 600mg at the time of this study. Using optimised ARV regimens can greatly increase the speed at which the 90–90–90 targets are achieved,

[29] World Health Organization. Transition to new antiretroviral drugs in HIV programmes: clinical and programmatic considerations [Internet]. Geneva: World Health Organization; 2017 (WHO/HIV/2017.23). [Cited 2018 Jan 23] Available from http://apps.who.int/iris/bitstream/10665/255887/1/WHO-HIV-2017.23-eng.pdf

by improving treatment outcomes through improved treatment adherence, viral suppression and improved quality of life of PLHIV (Sidibé et al., 2016).

Beck and colleagues in their comparison of STRs to MTRs among UK patients found that while the STR was as effective as the MTR of the same drugs, there would be cost savings of 20% at 6 months if the STR was started as the first line treatment. In addition to reducing treatment costs, STRs can improve treatment outcomes by reducing pill burden and improving adherence (Sebaaly and Kelley, 2017).

4.4 Adherence

Comparing number of missed pharmacy visits in Malta to that in Norway would result in bias. Since the required number of visits per person was higher in Malta, the number of missed pharmacy visits would also be higher. Instead, the proportion of missed visits was determined (Table 3.5) and a comparison was made between proportion of days covered between the two countries (Table 3.6).

Going by proportion of days covered (PDC), patients in Malta had comparable levels of adherence to patients in Norway, with 71% and 74% of patients having greater than or equal to 95% proportion of days covered, respectively. This level of adherence is considered suboptimal (Weiser et al., 2003), and is surprising given that ARVs are provided free of charge in Malta and Norway. Even though viral suppression has been observed in patients with 70% adherence, higher levels of ≥95 % are preferred (Kim et al., 2018).

Higher levels of adherence would be expected from both Malta and Norway because when medication is provided at no cost to the patient, an important barrier to ART nonadherence treatment is eliminated (Viswanathan et al., 2012). In one study, high cost of ARVs accounted for 17% of non-adherence.[30] The amount of out-of-pocket patient cost correlates linearly with the level of adherence (Eaddy et al., 2012), irrespective of patient income level (Piette et al., 2011).

A third of all patients in both countries missed their scheduled visit but most patients presented for a medication refill within 30 days. Less than 10% of patients in both countries went over 30 days without attending a scheduled pharmacy visit for ARV refill, 7% in Norway and 6% in Malta. This means that the majority of patients did not spend more than 30 days without ARV coverage. This is important because inconsistent adherence can result in development of viral resistance and a reversal of the benefits of effective ART, such as viral suppression and reduced risk of opportunistic infections. A study investigating the determinants of non-adherence to subsidised ART found that reasons for non-adherence included side effects, complexity of the treatment regimen, and stigma associated with family members discovering a patient's HIV status.

From this study, it would seem that the use of STRs did not confer any additional benefits in terms of adherence to the Norwegian patients over their Maltese counterparts. Simplifying ART regimens is often recommended for improving ART adherence (Chen et al, 2017) and many studies have shown that STRs and once-daily MTRs improved

[30] Boston Consulting Group. The hidden epidemic: finding a cure for unfilled prescriptions and missed doses [Internet]. BCG, 2003 [Cited 2018 May 15] Available from: http://www.bcg.com/documents/file14265.pdf

adherence (Bangsberg et al., 2010; Cooper et al., 2011). However other studies have shown mixed results concerning the benefits of STRs and once-daily MTRs. Two RCTs found that there was no difference in adherence when patients were switched from MTRs to STRs (Dejesus et al., 2009; Hodder et al., 2010). The other benefits of STRs should not be discounted, as they were associated with improved patient satisfaction and ease of use (Hodder et al., 2010), and studies continue to report that patients with a lower pill burden have better adherence and viral suppression. Patients on STRs also reported fewer side effects (Chen et al., 2017).

It is recommended that adherence to ART in Malta and Norway be measured using other measures of adherence other than the PDC method used in this study, to determine how the results obtained compare to results of this study. Other factors other than pill burden could also account for the observed adherence levels. Factors that can affect adherence include mental health, age, level of education and social support.

Among Norwegian patients, older age was associated with better adherence, with patients born in 1975 or before being more adherent than their younger counterparts. This finding is not in agreement with other studies which have found that adherence was greater among younger patients aged between 35 to 44 years (Letta et al., 2015). It would be worthwhile to investigate the observed association between age and ART adherence in Norwegian patients in future studies.

The PDC method was selected as a measure of adherence primarily because it did not require patient interviews. This ensured that patient identities were not disclosed in the

course of this study. The PDC method also carries an inherent ease of use because pharmacy records are routinely available, which made this method cost-effective.

Unlike patient self-report, PDC is free of recall bias, and does not require expensive devices such as electronic pill counters (Bangsberg 2008). The PDC method has been shown to correlate well with HIV treatment outcomes such as virologic suppression (Gachara et al., 2017). Sangeda et al. in their 2014 study reported that adherence measured using pharmacy refills outperformed patient self-reports. In their study, Sangeda and colleagues found that pharmacy refill adherence was the best method of predicting virologic failure when compared to patient self-report and pill count. An earlier cohort study had also found that pharmacy refill adherence measurements were as accurate as CD4 counts in detecting virologic failure (Bisson et al., 2008).

Malta and Norway had sufficient record keeping in form of the NorPD and the Mater Dei Pharmacy Dispensing database. In view of this and the above factors, PDC was considered a reliable method of assessing adherence to ART in Malta and Norway.

4.5 Pre-exposure Prophylaxis

While pre-exposure prophylaxis (PrEP) was provided free of charge in Norway, this policy is yet to be introduced in Malta. Data from key-informant interviews in Norway reported an increase in recent prescriptions of Truvada (tenofovir disoproxil fumarate + emtricitabine), the ARV regimen used for PrEP as well as treatment of HIV (when used in combination with other drugs). This increase in prescriptions was believed to be due

to the new policy of free PrEP in Norway. Quantitative data also showed that Truvada was the most commonly prescribed drug, representing 15.4% of all prescriptions.

The high cost of daily Truvada (tenofovir-emtricitabine) could be a limiting factor for implementing PrEP in government health systems (Krakower et al., 2015); this may be the reason as to why free PrEP has not yet been implemented in Malta. Nichols and colleagues posit that at the current drug prices and within the context of a stable HIV epidemic, at 80% effectiveness, PrEP may cost up to €11 000 per quality-adjusted life-year (QALY) gained when used daily, or only €2000 per QALY gained when used on demand.

In a survey conducted by the ECDC, European countries reported three main barriers to providing PrEP: cost of drugs, cost of service delivery and feasibility.[31] In this same survey, countries expressed concerns about the effect of PrEP use on transmission of other STIs. The PROUD clinical trial on PrEP use in the UK found no evidence of increased STIs among patients on PrEP (McComarck et al., 2016).

While the initial cost may seem high, PrEP has been found to be cost effective at the current ARV prices (Ross et al., 2016). Generic brands of tenofovir and emtricitabine are currently marketed, and this may lead to more widespread use of PrEP in Europe. The

[31] European Centre for Disease Prevention and Control. The status of the HIV response in the European Union/European Economic Area, 2016 [Internet]. Stockholm: ECDC; 2017 [Cited 2017 Aug 05]. Available from https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/Status-of-HIV-response-in-EU-EEA-2016-30-jan-2017.pdf

current price of generic tenofovir/emtricitabine is EUR 180 for 30 tablets compared to EUR 406 per 30 tablets for the originator brand, Truvada.[32] France, Norway and the Netherlands currently provide fully reimbursed PrEP; other European countries are considering starting PrEP pilot projects.[33] The advent of generic versions of Truvada ought to make providing PrEP cheaper for the national health service in Malta.

In the USA, Gilead Sciences, the manufacturer of Truvada, has a drug assistance program for uninsured patients in the US and will provide Truvada at no cost to qualified patients.[34] For individuals with insurance, many US insurers cover the cost of PrEP. [35] In France, Truvada was fully reimbursed by the healthcare system but clinic visits and tests were covered at the usual rate, which was 60% of costs reimbursed (McCormack et al., 2016). A model of subsidised cost for PrEP could be valuable in Malta, to provide PrEP while keeping costs manageable for both the health system and patient. McCormack et al. also report that this development in the French setting was a result of civil society pressure, and subsequently Ministry of Health funding. This speaks to the positive role that civil society groups and political will can play in advancing HIV care.

[32] Collins S. Generic PrEP in France and Scotland challenges access across the UK. HIV Treatment Bulletin [Internet]. HIV i-Base; 2017 [Cited 2018 June 02]. Available from http://i-base.info/htb/32501

[33] European Centre for Disease Prevention and Control (ECDC). Pre-exposure prophylaxis for HIV prevention in Europe [Internet]. Stockholm: ECDC; 2016 [Cited 2017 Aug 05]. Available from: http://ecdc.europa.eu/en/publications/Publications/pre-exposure-prophylaxis-hiv-prevention-europe.pdf

[34] Gilead Sciences - Paying for Truvada [Internet]. Gilead Sciences; 2018 [Cited 2018 Jan 25]. Available from http://www.truvada.com/truvada-patient-assistance

[35] Washington State Department of Public Health. Pre-Exposure Prophyalxis Drug Assistance Program (PrEP DAP) [Internet]. WA State DoPH. [Cited 2018 Jan 25]. Available from http://www.doh.wa.gov/YouandYourFamily/IllnessandDisease/HIVAIDS/HIVCareClientServices/PrEPDAP

There is some public interest in Malta concerning the provision of newer ART regimens and PrEP[36] and civil society groups have been vocal about the same issues.[37] This bodes well for the fight against HIV in Malta as public engagement is an important facet of public health. This notion is also reinforced in the Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia.

4.6 Procurement and cost reduction

Both Malta and Norway employed health technology assessment (HTA), reference pricing and price capping practices in the financing aspect of drug procurement. The procurement bodies in both countries negotiated prices with pharmaceutical companies to obtain favourable prices. Prices for ARVs were negotiated centrally in both countries, even though procurement was actually decentralised in Norway, given that distribution of ARVs to the final consumer is decentralised as well.

The procurement team at Mater Dei Hospital were in need of a good forecast of newer ARVs in use, however the clinical team could not supply an accurate forecast if newer ARVs were being saved for patients that experience treatment failure on older regimens. In such a scenario, the clinical team cannot predict which patients will experience treatment failure and require switching regimens.

[36] We should not fight people living with HIV, we should fight the virus. The Malta Independent. Published 2018 Feb 18 [Cited 02/06/2018]. Available from http://www.independent.com.mt/articles/2018-02-18/newspaper-opinions/We-should-not-fight-people-living-with-HIV-we-should-fight-the-virus-6736184953

[37] Gay rights groups propose new treatment and easier access to HIV medication. Malta Today. Published 2016 Nov 30 [Cited 02/06/2018]. Available at https://www.maltatoday.com.mt/lifestyle/health/72143/gay_rights_groups_propose_new_treatment_and_easier_access_to_hiv_medication#.WyFJyC2B0dV

In an effort to reduce costs of acquiring ARVs, at the time of this study both Malta and Norway were evolving the procurement mechanisms used to ensure medicines are purchased at as low a cost as possible. Malta was improving internal systems to facilitate better forecasting of drug needs and introducing a new procurement system, "the package deal" earlier described. Norway was shifting to a tender system of procuring ARVs in favour of the old system that was deemed costlier.

4.7 Implication of findings

The low use of newer ARVs in Malta does not bode well for the elimination of HIV in Malta. The findings of this study support the case for an immediate update of the formulary for antiretroviral drugs at Mater Dei Hospital. Newer antiretroviral drugs, even though named so, have been in use since 2005 (Bayoumi, 2013). For a condition, such as HIV, whose treatment is constantly evolving for the better, 12 years can be considered to be a long time to maintain a formulary without updates that reflect the advances of evidence-based medicine in the treatment of HIV/AIDS.

Going by the findings of this study, it is reasonable to extrapolate that HIV patients in Norway are less likely to discontinue treatment due to adverse events, as newer ARVs have been shown to have a lower rate of discontinuation (Rockstroh et al., 2013). Health care professionals interviewed in Malta were aware of the current HIV/AIDS treatment guidelines, and expressed frustration over the inability to provide the superior newer ARVs to patients. This would suggest that there are other factors at play, probably at the policy-making level, that have inhibited the evolution to newer ARVs in Malta to make

them the norm, and not the exception. Exploring these system-level factors could provide insight into why it has taken Malta so long to roll out newer ARVs for all eligible patients.

Political will could be an important factor worth exploring, to identify its impact on HIV care in Malta. Findings of this study showed that advances have been made in other areas of treatment at Mater Dei Hospital, such as oncology, because it was a political priority. Great strides were also made in Hepatitis C care, because it was a political priority for the infectious diseases department at the time. Similar political interest in HIV in Malta would further the cause of the infectious diseases department at Mater Dei Hospital to provide the best internationally available standard of care to HIV patients.

PEPFAR, the U.S. President's Emergency Plan for AIDS Relief founded in 2003 is a prime example of the influential role of political will and leadership in advancing HIV/AIDS treatment. Clinical and public health interventions to eliminate HIV can be significantly improved with the strategic support of political leaders (Karan et al., 2017).

Newer ARVs are expensive (Bayoumi, 2013) and that could be an important factor that has limited their adoption on to the formulary and subsequent widespread use in Malta. While the cost of newer ARVs per se is quite high, using newer ARVs is in the long run cost-effective to health systems. It has been estimated that transitioning to new lower cost ARV drugs in HIV treatment programmes in low- and middle-income countries could save more than US$ 1 billion in health budgets by the end of 2025.[38]

[38] Transition to new antiretroviral drugs in HIV programmes: clinical and programmatic considerations [Internet]. Geneva: World Health Organization; 2017 (WHO/HIV/2017.23) [Cited

Malta and Norway both use generic and innovator brand ARVs. This is important for cost reduction, as studies have shown that using generic ARV brands can significantly reduce cost of HIV treatment in the developed world (Rwagitinywa et al., 2018). Rwagitinywa and colleagues found that increased utilisation of low-price generic ARVs in Denmark was associated with overall savings on treatment cost. Taking into consideration patient factors, increasing the use of generic brand ARVs in Malta and Norway can provide even greater cost-savings that can go towards providing newer ARVs for all eligible patients

A significant observation made during this study was that some pharmaceutical companies acquire a marketing authorisation (MA) in Malta to be able to trade all across the EU, but then do not supply their products in Malta, possibly because of the small market size and limited financial benefit to the pharmaceutical company. This is true for companies that manufacture ARVs and hold MAs in Malta. While there is a financial benefit to Malta in terms of the fees paid by the pharmaceutical company to obtain and keep a MA in Malta, the Maltese health care system suffers high costs involved in procuring medicines that would otherwise be cheaper to provide if these same pharmaceutical companies supplied the Maltese market. Ultimately the patient suffers too, as the health care system will prioritise based on cost which means that the newer, more expensive ARVs will not be readily available to patients. As a result, patients will

02/06/2018] Available from http://apps.who.int/iris/bitstream/handle/10665/255887/WHO-HIV-2017.23-eng.pdf;jsessionid=A9C2884AA60331BD8208F42DF73BF667?sequence=1&TSPD_101_R0=bfe42e1d5f664504b941c2bbcfe61cc6m3w0000000000000002cc8dd550ffff0000000000000000000000000000005b97f4a7001bc80e76

be kept on the older and less expensive treatment options, and not the newer more expensive and more effective alternatives.

4.8 Limitations of the study

PDC as a measure of adherence relies on pharmacy data, and does not take into account hospitalisations during which a patient could use in-patient prescribed drugs instead of the drugs already in the patient's possession. PDC is also insensitive to the possibility that a patient may carry over remaining drugs from a previous treatment interval into a new refill interval.

This data obtained could not be used to make comparisons between Malta and Norway on patient variables such as gender, age, and ARVs brands used, as this information is not routinely recorded at the pharmacy level dispensing database in Malta.

The prescription and dispensing data did not contain any information on deaths, emigration, long stays in hospital or transfer to permanent residence in a nursing home. This would have resulted in loss to follow-up and may have biased the adherence downwards (poorer adherence than the true adherence). All patients included have at least 180 days of follow-up, but some have more. The study period of 18 months is relatively short considering that ART is lifelong treatment. It is therefore not possible to predict the long-term behaviour of patients with regards to adherence.

The importance of cost as a factor determining availability of ARVs was recognised, however this study could not compare cost of ARVs in Malta to that in Norway. In

Norway, the law requires prices of medicines to be availed publicly in order to ensure transparency. Data on the cost of ARVs in Norway was obtained for this study, but data on prices for ARVs in Malta was not available, due to confidentiality agreements between the procuring body and the pharmaceutical companies. Consequently, a comparison could not be made on the cost of ARVS between the two national health systems.

The difference between medicines regulation and health provision in the two countries presented a challenge in the conduct of this study, especially on the qualitative arm of the study. The Norwegian Medicines Agency plays a central role in determining prices for drugs procured in Norway, alongside the national procurement body, Sykehusinnkjøp therefore individuals from these organisations were the respondents in the key-informant interviews. The corresponding regulatory authority in Malta, the Malta Medicines Authority does not play a role in pricing for pharmaceuticals, nor their procurement and as a result, no participants were obtained from here. Key-informant interviews were conducted with the Central Procurement and Supplies Unit staff instead, and pharmacists at Mater Dei Hospital.

4.9 Recommendations

Policies should be put in place in which companies that manufacture ARVs and possess a MA in Malta should distribute these products in Malta. This would potentially facilitate procuring of ARVs and reduce costs.

It is recommended to enforce mandatory periodic updates of the ARV formulary at Mater Dei Hospital, to keep up-to-date with advances in HIV treatment, and develop protocol relevant to the Maltese setting on how to transition from the older drugs to the newer ARVs. Patients in both Malta and Norway should be transitioned to regimens that have been proven to be more beneficial, for example for patients on regimens containing efavirenz, efavirenz 400mg is more tolerable than efavirenz 600mg. These changes should take into account patient-specific factors when selecting treatment. It is also recommended that pharmacy records at Mater Dei Hospital should record patient gender and age.

Further investigation in to the adherence patterns of patients on ART in Malta and Norway is recommended, as adherence would have been expected to be higher in Norway where prescriptions of STRs were more predominant (32.8% N= 38605) compared to 0% (N=5657) in Malta. Higher adherence levels would also be expected from both countries as there were no financial barriers to adherence for the patients.

The practice of providing free PrEP in Norway is a good initiative that can further the decline in HIV cases observed in MSM in Norway. Introducing free PrEP in Malta could result in reduced HIV incidence, as Malta's greatest increase in new HIV cases was found to be in MSM. Given the vast evidence proving the cost-effectiveness of PrEP as well as its effectiveness in reducing the risk of HIV transmission, it is not a sound public health policy for Malta to not provide free PrEP to at-risk patients. The absence of PrEP is counter-intuitive to cost-saving efforts in Malta's HIV treatment programme, since PrEP has been shown to lead to long-term cost savings.

Norway could stand to benefit from procurement practices that can reduce the cost of ARVs to the health system, such as tenders and bidding. Pooled procurement solutions to increase volume of purchases and lower drug costs would benefit both Norway and Malta, given the small ARV market size of both countries.

4.10 Conclusion

This study investigated availability of antiretroviral drugs (ARVs), adherence to ART and factors associated with availability of ARVs in Malta and Norway, and found that newer ARVs and single-tablet regimens were more predominantly used in Norway than Malta. Malta and Norway had the same proportion of patients that achieved optimal adherence at PDC $\geq$ 0.95; with 74% of patients in Malta and 71% of patients in Norway achieving this desired adherence level. The higher use of newer ARVs and single tablet regimens in Norway did not seem to confer advantages in terms of adherence to the Norwegian patients over the Maltese patients.

This study identified barriers to availability of newer ARVs that need to be addressed. In both countries, the small market size and procurement mechanisms in use kept the cost of procuring ARVs high. Political will to provide the current standard of ART was more favourable in Norway than Malta. Prescribers in Norway did not have any restrictions to the type of ARVs prescribed, while prescribers in Malta were limited to prescribing the older ARVs listed on an out-dated formulary.

Findings showed that PrEP is provided free of charge in Norway but not provided in Malta. In view of Statement 16 of the Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia[39] which states that European countries will "control the incidence and prevalence of sexually-transmitted infections, particularly amongst those at the highest risk of and most vulnerable to HIV/AIDS, through increased public awareness of their role in HIV transmission, improved and more accessible services for prompt diagnosis and efficient treatment;" it is important that all European countries, including Malta start to provide fully reimbursed PrEP to at-risk individuals, starting with MSM since HIV transmission among MSM has been on the rise.

In conclusion, better policies that promote the availability and use of newer ARVs in Malta need to be implemented, and efforts should be made to improve adherence to ART in Malta and Norway.

[39] Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia [Internet]. Dublin: World Health Organisation; 2004 [Cited on 02/06/2018]. Available from http://www.euro.who.int/en/health-topics/communicable-diseases/hivaids/policy/guiding-policy-documents-and-frameworks-for-whoeuropes-work-on-hiv/dublin-declaration-on-partnership-to-fighthivaids-in-europe-and-central-asia

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APPENDICES

APPENDIX 1

Appendix 1: Ethics Approval

L-Università ta' Malta

Faculty of
Medicine & Surgery

University of Malta
Msida MSD 2080, Malta

Tel: +356 2340 1879/1891/1167
umms@um.edu.mt

www.um.edu.mt/ms

Ref No: **62/2017**

Dear Ms. Catherine Namulindwa,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

The availability of antiretroviral drugs and associated factors: a comparison between Malta and Norway

The University Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

APPENDIX 2

Appendix 2: Norwegian Institute of Public Health Approval

folkehelseinstituttet

Universitetet i Bergen
v/ Lone Holst
Avd. for global helse og samfunnsmedisin
Kalfarveien 31
5018 Bergen

Vår ref: 17/11661/HDHU/OLFE
Dato: 29.9.2017

Utlevering av data fra Reseptregisteret

Det vises til søknad datert 21.8.2017 om data fra Reseptregisteret til prosjektet «Availability of antiretroviral drugs and associated factors: A comparison between Malta and Norway» (PDB 2312).

Folkehelseinstituttet har vurdert søknaden og funnet at prosjektet ligger innenfor formålet med Reseptregisteret (jf. reseptregisterforskriften § 1-3) og at øvrige vilkår for utlevering er oppfylt.

Datamaterialet
Datamaterialet består av følgende semikolonseparerte excelfil:

- *2312_Reseptregisterdata_201709*
  Filen inneholder utleveringer av legemidler med følgende ATC-koder: J05AR01, J05AR02, J05AR03, J05AR04, J05AR05, J05AR06, J05AR07, J05AR08, J05AR09, J05AR10, J05AR11, J05AR12, J05AR13, J05AR14, J05AR15, J05AR16, J05AR17, J05AR18, J05AR19, J05AE01, J05AE02, J05AE03, J05AE04, J05AE05, J05AE07, J05AE08, J05AE09, J05AE10, J05AF01, J05AF02, J05AF03, J05AF04, J05AF05, J05AF06, J05AF07, J05AF09, J05AF13, J05AG01, J05AG02, J05AG03, J05AG04, J05AG05, J05AX07, J05AX08, J05AX09, J05AX11, J05AX12 og V03AX03 i perioden 1.1.2016 – 30.6.2017. Det var ikke registrert utleveringer for alle de omsøkte ATC-kodene i perioden. For hver utlevering inneholder filen følgende variabler: PasientLopeNr, PasientFodtAr_gruppert, PasientKjonn, PasientBostedHelseregionNavn (Helseregion Vest / Øvrig helseregion / Ukjent Helseregion) UtleveringsDato, OrdinasjonAntallPakninger, OrdinasjonAntallDDD, VareNavn, VarePakningStr, VarePakningEnhet, VarePakningStyrke, ATCKode, ATCKodeDDDVerdi, ATCKodeDDDEnhet, VarenrAUP. Filen består av 38 605 rader.

Det er benyttet ATC/DDD-versjon 2017. Tallmaterialet fra Reseptregisteret er basert på resepter med komplette, korrekte fødselsnummer, dvs. pasienter hvis legemiddelhistorikk kan følges. Reseptregisteret inneholder en liten andel resepter hvor fødselsnummer enten mangler eller er feil registrert (0,30 % i 2016), så tallene må betraktes som minimumstall.

Videre minnes det om at data fra Reseptregisteret ikke inkluderer individdata for legemidler utlevert på institusjon (f.eks. sykehus/sykehjem).

Folkehelseinstituttet
Postboks 4404 Nydalen
Sandakerveien 24C
Tlf: 21 07 81 00
folkehelseinstituttet@fhi.no
www.fhi.no
Helsedata og digitalisering
Avdeling for helseundersøkelser

Nødvendige tillatelser og hjemmelsgrunnlag
Utleveringen skjer med hjemmel i reseptregisterforskriften § 5-2.

Vilkår for utlevering:

- Opplysningene skal kun brukes til formål som angitt i søknaden. Hvis opplysningene ønskes brukt til andre formål, må det søkes på nytt om dette.
- Opplysningene skal ikke overlates til andre enn prosjektmedarbeidere som er oppgitt i søknaden. Alle som mottar datasettet har taushetsplikt i henhold til helseregisterloven § 17. Hvis nye medarbeidere trenger tilgang til datafilen skal dette meldes til Reseptregisteret, Folkehelseinstituttet.
- Opplysningene skal oppbevares betryggende og på en slik måte at uvedkommende ikke får tilgang til dem, og ellers i samsvar med sikkerhetsbestemmelsene i personopplysningsforskriftens kapittel 2.
- Publisering og annen offentliggjøring skal gis i en slik form at enkeltpersoner eller apotek ikke kan identifiseres.
- Datamaterialet skal slettes senest innen prosjektets avslutning 31.07.2018, jf. reseptregisterforskriften § 5-2. Skriftlig bekreftelse på at materialet er slettet skal oversendes Reseptregisteret, Folkehelseinstituttet.
- Ved publisering eller offentliggjøring skal Reseptregisteret (NorPD) ved Folkehelseinstituttet angis som kilde. I alle publikasjoner skal «Reseptregisteret» eller «The Norwegian Prescription Database» inngå i tittel eller abstract-tekst av hensyn til PubMed-søk.
- Folkehelseinstituttet er ikke ansvarlig for tolkninger eller analyser av dataene som blir gjort av andre.

Fakturering:
I henhold til reseptregisterforskriften § 5-5 kan Folkehelseinstituttet kreve dekket faktiske utgifter som påløper i forbindelse med behandling og tilrettelegging av opplysninger knyttet til konkrete oppdrag. Faktura pålydende kr. 13 125,- ekskl. mva. sendes separat.

Kontaktinformasjon:
Reseptregisteret kan kontaktes per e-post (reseptregister.data@fhi.no), telefon (21 07 70 00, FHIs sentralbord) eller brevpost (Folkehelseinstituttet, Reseptregisteret, Pb 4404 Nydalen, 0403 OSLO).

Vennlig hilsen

Åsa L'Abée-Lund
Avdelingsdirektør

Olaug Fenne
Seniorrådgiver

APPENDIX 3

Appendix 3: Key Informant Interview (Malta)

Interviewee ID code: ---------- Profession: ---------- Date: -------

PART A

1. Who is responsible for procuring antiretroviral drugs (ARVs) at Mater Dei Hospital?

2. What factors are considered when procuring ARVs?

3. What price reduction strategies are used in procuring ARVs?

4. Which pooled procurement schemes is Malta a part of?

5. How do prices of ARVs in Malta compare to international reference prices?

6. Which companies supply ARVs in Malta?

7. Are generic forms of ARVs distributed in Malta?

8. If yes, which specific ARV drugs have generic forms distributed in Malta?

9. What antiretroviral drugs are locally produced in Malta?

PART B

1. Which of the below categories best describes the main external source of supply of antiretroviral drugs in Malta?

I. Originator
II. Generic company
III. Other – explain

2. Have you experienced any problems with sourcing some antiretroviral drugs in the past year?
3. If yes, from which category of supplier do you most frequently encounter problems with sourcing specific antiretroviral medicines?

4. Can you recall a time when there was a shortage of antiretroviral medicines?
5. In your experience, how long would you estimate the average or typical antiretroviral medicines shortage normally lasts for?
    i. A number of months
    ii. A number of weeks
    iii. a number of days

6. What is the longest duration that you can recall a medicine being in shortage for?
7. Is there a written protocol for dealing with non-availability of antiretrovirals drugs?
8. What actions are taken to minimise the impact of non-availability of antiretroviral drugs?

PART C

1. Who pays for antiretroviral drugs?

2. If patients get the drugs free, are they free at point of care, or do patients pay for them then get reimbursed later?
3. Is a co-payment required from the patient for antiretroviral drugs?

4. Are HIV-related drugs free to patients?

PART D

1. What system is in place to provide antiretroviral pre-exposure prophylaxis (PREP) to at-risk individuals?
2. How are these at-risk individuals recruited for PREP?
    i. Voluntary
    ii. Active recruitment initiatives
    iii. Health care provider initiated
3. To which individuals is PrEP available?
4. If available, is PrEP free?
5. What more comments can you make regarding the availability of antiretroviral drugs in Malta?

APPENDIX 4

Appendix 4: Key Informant Interview (Norway)

Interviewee ID code: ---------- Profession: ---------- Date: -------

PART A

1. Who is responsible for procuring antiretroviral drugs (ARVs) in Norway?

2. What factors are considered when procuring ARVs?

3. What price reduction strategies are used in procuring ARVs?

4. Which pooled procurement schemes is Norway a part of?

5. How do prices of ARVs in Norway compare to international reference prices?

6. Which companies supply ARVs in Norway?

7. Are generic forms of ARVs distributed in Norway?

8. If yes, which specific ARV drugs have generic forms distributed in Norway?

9. What antiretroviral drugs are locally produced in Norway?

PART B

1. Which of the below categories best describes the main external source of supply of antiretroviral drugs in Norway?
    I. Originator
    II. Generic company
    III. Other – explain

2. Have you experienced any problems with sourcing some antiretroviral drugs in the past year?

3. If yes, from which category of supplier do you most frequently encounter problems with sourcing specific antiretroviral medicines?
4. Can you recall a time when there was a shortage of antiretroviral medicines?

5. In your experience, how long would you estimate the average or typical antiretroviral medicines shortage normally lasts for?
    I. A number of months
    II. A number of weeks
    III. a number of days

6. What is the longest duration that you can recall a medicine being in shortage for?
7. Is there a written protocol for dealing with non-availability of antiretrovirals drugs?
8. What actions are taken to minimise the impact of non-availability of antiretroviral drugs?

PART C

1. Who pays for antiretroviral drugs?

2. If patients get the drugs free, are they free at point of care, or do patients pay for them then get reimbursed later?
3. Is a co-payment required from the patient for antiretroviral drugs?

4. Are HIV-related drugs free to patients?

PART D

1. What system is in place to provide antiretroviral pre-exposure prophylaxis (PREP) to at-risk individuals?
2. How are these at-risk individuals recruited for PREP?
    I. Voluntary
    II. Active recruitment initiatives
    III. Health care provider initiated
3. To which individuals is PrEP available?
4. If available, is PrEP free?
5. What more comments can you make regarding the availability of antiretroviral drugs in Malta?

APPENDIX 5

Appendix 5: Questionnaire Validation Tool

This will be a 15-minute exercise to determine the content representativeness of the elements of the attached questionnaire.

The attached questionnaire is meant to determine the following.

1. Procurement practices
   - Responsible body/bodies
   - Factors determining what is procured
   - Participation in pooled procurement schemes
   - Comparability of antiretroviral prices to international reference prices
   - Types of pharmaceutical companies from which ARVs are procured – originator or generic?
   - Presence of locally manufactured ARVs
2. Shortage of antiretrovirals
   - Predominant source of ARVs – originator or generic?
   - Frequency of shortages
   - Duration of shortages
   - How shortages are dealt with
3. Payment for antiretroviral drugs
   - Who pays?
4. Availability of pre-exposure prophylaxis
   - To whom is PrEP available?
   - Is PrEP free?

The questionnaire respondents will be pharmacists and physicians.

Please grade each question in the questionnaire on a scale of 1-4 according to its degree of relevance to the study. Write the grade next to the question. Use the table below for guidance.

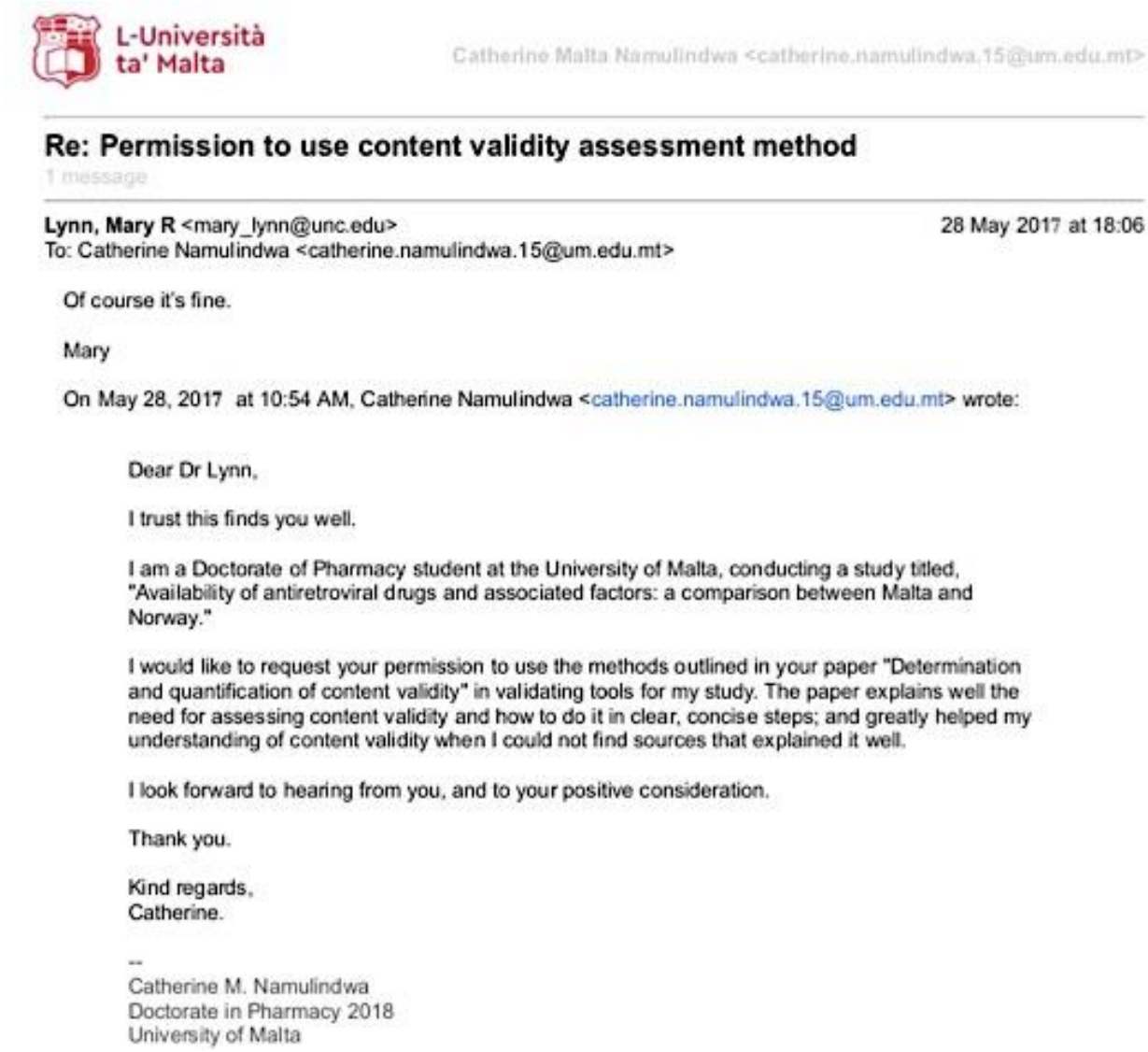
Rating Scale	Relevance interpretation
1	Not relevant
2	Unable to access relevance without item revision
3	Relevant but needs minor alterations
4	Very relevant and succinct

©Mary R. Lynn, PhD. Determination and quantification of content validity.

- If you give the question a grade of 2 or 3, kindly provide a suggestion on how the question can be revised to make it valid and relevant.
- If you identified any relevant areas that have been omitted from the questionnaire, please list them at the end of the questionnaire.

APPENDIX 6

Appendix 6: Approval to use Validation Method



L-Università ta' Malta

Catherine Malta Namulindwa <catherine.namulindwa.15@um.edu.mt>

Re: Permission to use content validity assessment method

1 message

Lynn, Mary R <mary_lynn@unc.edu> 28 May 2017 at 18:06
To: Catherine Namulindwa <catherine.namulindwa.15@um.edu.mt>

Of course it's fine.

Mary

On May 28, 2017 at 10:54 AM, Catherine Namulindwa <catherine.namulindwa.15@um.edu.mt> wrote:

> Dear Dr Lynn,
>
> I trust this finds you well.
>
> I am a Doctorate of Pharmacy student at the University of Malta, conducting a study titled, "Availability of antiretroviral drugs and associated factors: a comparison between Malta and Norway."
>
> I would like to request your permission to use the methods outlined in your paper "Determination and quantification of content validity" in validating tools for my study. The paper explains well the need for assessing content validity and how to do it in clear, concise steps; and greatly helped my understanding of content validity when I could not find sources that explained it well.
>
> I look forward to hearing from you, and to your positive consideration.
>
> Thank you.
>
> Kind regards,
> Catherine.
>
> --
> Catherine M. Namulindwa
> Doctorate in Pharmacy 2018
> University of Malta

APPENDIX 7

Appendix 7: Information Sheet and Consent Form

Study Title: Availability of antiretroviral drugs and associated factors: a comparison between Malta and Norway

Information sheet

My name is Catherine Namulindwa; I am conducting research on the availability of antiretroviral drugs and associated factors. This will be a comparative study between Malta and Norway. This study is being conducted in partial fulfilment of the award of the Doctorate of Pharmacy degree.

This survey is designed to collect data on the availability of antiretroviral drugs in Malta and Norway, as well as the factors that may affect the availability of these drugs. Healthcare professionals involved in the procurement of antiretroviral medicines and the provision of antiretroviral therapy are invited to participate, as well as professionals from the medicines regulatory authorities.

The survey includes questions on procurement and distribution of antiretroviral medicines. The results of the study will be evaluated by the researcher and used to make recommendations in promoting access of antiretroviral drugs to patients.

Your participation in the study is completely voluntary and you are free to withdraw from this study at any time.

Your responses will be recorded on a digital recorder, and will be kept confidential and only be presented in aggregate. There may be use of quotations from your responses; however, these will be reported anonymously. Participant identities will be kept confidential and all recordings will be destroyed upon completion of the study. Should you have any questions, please feel free to contact Catherine Namulindwa on +356 99331207 in Malta or +47 93442635 in Norway. You can also email catherine.namulindwa.15@um.edu.mt.

Thank you for your time. By participating in the interview, you acknowledge that you have read this information and agree to participate in this research, with the knowledge that you are free to withdraw your participation at any time without penalty.

Please write your initials below to indicate that you have read the above information.

---------- Date: ----------

Study Title: Availability of antiretroviral drugs and associated factors: a comparison between Malta and Norway

Consent Form

I, ... confirm that I voluntarily agree to participate in the study "Availability of antiretroviral drugs and associated factors: a comparison between Malta and Norway."

I confirm that I have read and understood the attached information.

I understand that I am free to withdraw my consent at any time.

Signature: .....

Date: .....

APPENDIX 8

Appendix 8: Dispensing Data Collection Sheet

Patient's project ID
Patient's birth year
Patient's sex
Dispensing date
ATC code
Brand name
Drug strength
DDD value
Number of DDDs
Number of packages
Package size
Pharmacy retail price

APPENDIX 9

Appendix 9: Funding for data collection from NorPD and statistical analysis

Subject	**RE: Question from Catherine and Lone**
From	Bente Elisabeth Moen <Bente.Moen@uib.no>
To	Lone Holst <Lone.Holst@uib.no>
Copy	Catherine Namulindwa <Catherine.Namulindwa@uib.no>
Date	2018-04-10 20:38

Hello - I think you both are associated with CIH, and we are willing to pay a max of 10 000 for you statistical help in 2018. (Please mention us in publications!)
You need to ask Jannicke to send her bill to CIH, to be paid by "SIH satsninger" -analysenummer 238728.
Good luck from Bente

-----Original Message-----
From: Lone Holst
Sent: Tuesday, April 10, 2018 3:45 PM
To: Bente Elisabeth Moen <Bente.Moen@uib.no>
Cc: Catherine Namulindwa <Catherine.Namulindwa@uib.no>
Subject: Question from Catherine and Lone

Dear Bente,

Catherine is working hard on her thesis and her courses in Malta.
We have run into some problems with statistics and got some advice from Jannicke Igland (the "free 2 hours" of help offered by the statisticians at IGS) - see below. She can help, but it costs.

After the reorganisation of IGS I have no money (my "fagområde" has made a budget and every "krone" is spent), so my only choice is to ask you if CIH can help?
According to Jannicke "The current price is 829 NOK per hour and I think it will require 8-10 hours of work." Can you help Catherine or can you suggest another source of money for this?

Subject	**RE: SV: Data from the Norwegian Prescription Database**
From	Lone Holst <Lone.Holst@uib.no>
To	Catherine Namulindwa <Catherine.Namulindwa@uib.no>
Date	2017-08-17 09:39

- Thesis Proposal_0817_commLH170817.docx (50 KB)

Dear Catherine,

Great news!
Sorry, I was so busy yesterday but I managed to send an e-mail to Bente Moen and she has promised to pay the bill if we get it before mid-November (which we should definitely be able to do). This means that we can submit the application ASAP.

Do I have the latest version of your project plan? NorPD ask for it. The one I got on Friday has some "track changes" in it. Please see attachment - I have tried to fix it up a bit, but not completely. Please get back to me as soon as you have a "clean" version which I can submit.

Yes, the point about "self-prescription" will just have to be a "limitation". Maybe we should have a chat with them about how wide-spread they expect this to be? And you can ask the NoMA as well about their thoughts on the topic.

See you,
Lone

-----Original Message-----
From: Catherine Namulindwa
[mailto:Catherine.Namulindwa@uib.no]
Sent: Tuesday, August 15, 2017 1:58 PM

APPENDIX 10

Appendix 10: Conference presentations

Norwegian Forum
for Global Health Research

Confirmation – participation with poster at Global Health Conference 2018

This is to confirm that **Catherine Namulindwa** from **the University of Malta** attended the Norwegian Global Health Conference "Health systems strengthening - Health for all revisited" Oslo 10-11 April 2018.

Namulindwa submitted the abstract "**Availability of antiretroviral drugs and associated factors: a comparion between Malta and Norway**".
The abstract was accepted as poster, and Namulindwa presented the poster at the conference.

The Norwegian Forum for Global Health Research was responsible for the scientific assessment of the poster.

Best regards

Gunhild Koldal
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Availability of antiretroviral drugs and associated factors: a comparison between Malta and Norway

Catherine M. Namulindwa[1], Janis Vella[1], Anthony Serracino-Inglott[1]

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Objectives

- To compare the availability of antiretroviral drugs (ARVs) in Malta and Norway
- To determine the factors associated with availability of ARVs

Background

- Reports indicate poor availability of newer ARVS in Malta
- Newer ARVs have been shown to be more tolerable and achieve faster viral suppression
- Effective HIV treatment and pre-exposure prophylaxis (PrEP) are useful for limiting HIV transmission

Incidence of HIV (rates per 100 000 population)					
	2012	2013	2014	2015	2016
Malta	7.2	8.5	9.4	14.2	14.5
Norway	4.9	4.6	5.2	4.3	4.2

Table 1. Comparison of HIV incidence between Malta and Norway

Norway

- Greatest decline in HIV in 10 years first reported in 2015, an even lower rate reported in 2016
- Greatest decline was in men who have sex with men (MSM)

Malta

- One of 3 countries with the highest rates of new HIV cases in 2016: 14.5 per 100 000 population
- Rate has more than doubled in past decade, from 5.9 in 2006
- Greatest increase was in MSM

Methods

Quantitative

- ARV dispensing data from Mater Dei Hospital dispensing database in Malta and the Norwegian Prescription Database

Qualitative

- Key informant interviews with pharmacists involved in dispensing and procuring ARVs in Malta and Norway

Findings

	Malta	Norway
Number of patients	361	5282
Newer ARVs	4.9%	23.4%
Number of ARVs	19	44
Drug regimens used	Only multiple pill regimens	Single-tablet regimens widely used - 32.8%
Availability of PrEP	Not provided	Provided free of charge

Table 2. Quantitative findings of the study

Factors associated with availability of ARVs

Malta

HIV treatment is centralised and free of charge. An outdated formulary, challenges in drug forecasting and absence of HIV-allocated funding hamper availability of newer ARVs. The small market size raises ARV costs.

Norway

HIV treatment is decentralised and free of charge. High willingness to pay and political will favour availability of newer ARVs, however the small market size raises the cost of ARVs to health system.

Conclusion

- Newer ARVs are more predominantly used in Norway than in Malta, as Malta faces more challenges in availing newer ARVs.
- Norway's free PrEP policy can lead to further decline in HIV cases seen in MSM. Free PrEP in Malta could lower HIV rates, as Malta's greatest HIV increase is in MSM.
- Both Norway and Malta could benefit from procurement mechanisms that lower the cost of ARVs

Acknowledgements

Center for International Health, University of Bergen.

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University of Malta
L-Università ta' Malta