The Effect of Socioeconomic, Patient, and Logistic Determinants on Antiretroviral Pre-Treatment Drug Resistance

A Regression Analysis Model

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Popular Summary

HIV is a virus that can cause a syndrome called Acquired Immune Deficiency Syndrome (AIDS). HIV/AIDS compromises the immune system and the body's ability to fight off infections. HIV can be transmitted by exchange of body fluid from infected person e.g blood, semen and vaginal discharge. HIV does not transmit by daily human contact e.g hand shaking ,kissing or hugging. It cannot be cured, but with the help of drugs the virus can be controlled. When the virus changes its structure, it can cause the drug to stop working, meaning that the virus becomes resistant to the drug. This affects the effectiveness of treatment regimens and increases the risk of transmission. Drug resistance also worsen the patient's quality of life and make them prone to infections. Those infections can be lethal because the body cannot fight them anymore. There are many factors affecting the drug resistance. Some of those factors have been included in this study. Taking the medication on time, the availability of the medication and if the person took the medication for intermittent period of time those are the factors were studied. Also this study tried to understand the effects of how much a government spends on health care, and the human development index (a country's status in health care, education and income) on the development of drug resistance. The results showed that expensive medications that are not commonly used have higher levels of resistance in richer countries. While for older medications it was shown that interrupted usage increased the level of resistance.

Abstract

Introduction Human immunodeficiency virus (HIV) is a double stranded RNA retrovirus. According to the World Health Organization more than 30 million individuals were estimated to have HIV by the end of 2020, about 60% of which are in the African region. Pre-treatment drug resistance (PDR) can be defined as the resistant virus strains transmitted at the time of infection or acquired during previous exposure to ARV. This study asses the effect of drivers in PDR.

Method: This study was conducted with data extracted from published, publicly available data bases and reports by international organizations. The main sources were United Nation data bases and published reports from World Health Organization. Inferential statistics were used to assess the PDR to anti-retroviral drugs. A linear regression model was used to investigate the association between PDR and previous exposure to anti-retrovirals and anti-retroviral therapy, pre-exposure prophylaxis, national health expenditure, human development index, and drug stock-out for different classes of anti-retroviral drugs.

Results: The result indicated that NNRTI drug resistance was most common, and seven out of 29 countries had PDR to all four drug classes. The human development index was positively associated with INSTI and PI PDR ($p<0.05$), while NNRTI and NRTI were mainly positively associated with previous exposure to anti-retrovirals.

Conclusion This study assessed the impact of socio-economics determinants (human development index and national health expenditure), drug logistic determinants (stock-out), and patients' determinants (adherence and previous exposure to any kind of anti-retrovirals) on PDR. For expensive drug classes (PI and INSTI) the resistance was positively associated with human development index. Previous exposure to anti-retrovirals was associated with increased resistance in NNRTI and NRTI.

Key words: HIV, Pre-treatment drug resistance, Antiretroviral, socioeconomic determinants, HDI, PrEP.

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Abbreviation

AVAC	AIDS Vaccine Advocacy Coalition
HDI	Human Development index
HIV	Human immunodeficiency virus
INSTI	Integrase strand transfer inhibitor
NHE	National Health Expenditure
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PDR	Pre-treatment drug resistance
PI	Protease inhibitor
PrEP	Pre-exposure Prophylaxis
WHO	World Health Organization

Introduction

Human immunodeficiency virus (HIV) is a double stranded RNA retrovirus. It attacks the immune system, specifically $CD4^+$ T-cells, compromising host immunity by decreasing the $CD4^+$ T-cells count. This subsequently leads to a loss of defence mechanism and makes the body susceptible to opportunistic infections and cancer [(1)]. HIV infection is prevented by limiting the risk of exposure, and the adoption of protective measures and behaviours. Condom use and pre-exposure prophylaxis (PrEP) are preventative measures that are recommended to be used to reduce to the risk of infection [(2)].

HIV infection is a troublesome issue to global public health; according to the World Health Organization more than 30 million individuals were estimated to have HIV by the end of 2020, about 60% of which are in the African region [(3)]. The sustainable development goal 3.3 states: "*By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases.*" [(4)].

Effective treatment is playing a crucial role in controlling and ending the HIV epidemic [(5)]. Currently there is no cure for HIV, but the virus levels in the host can be suppressed by anti-retroviral (ARV) drugs. HIV transmission is related to the virus load; the lower the load the lower the risk of transmission [(2)]. Anti-retroviral therapy (ART) which is a combination of different ARVs; also decreases the morbidity and mortality associated with the infection. Since 2016, the WHO recommends to initiate treatment with lifelong ART for all people living with HIV, regardless of $CD4^+$ counts or age [(3)]. To achieve the SDG 3.3 goals, effective treatment must be ensured to all people living with HIV as soon as they are diagnosed.

ARV drugs are a cornerstone in combating HIV epidemic. There are different pharmacological classes of ARV. Each class targeted different step in HIV life cycle. In this study we focused on the main four classes that are commonly used in ART regimen (table 1).

Table 1 Pharmacological classes of Antiretroviral and their mechanism of actions(6)

Pharmacological Class	Mechanism of action	Drugs
Nucleoside reverse transcriptase inhibitors (NRTI)	bind to the HIV reverse transcriptase enzyme	· Abacavir (ABC); Emtricitabine (FTC), Lamivudine (3TC); Stavudine (D4t), Tenofovir Alafenamide Fumarate (TAF), Tenofovir Disoproxil Fumarate (TDF), Zidovudine (AZT).
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	bind to the HIV reverse transcriptase enzyme	Doravirine (DOR), Efavirenz (EFV), Etravirine (ETR), Nevirapine (NVP), Rilpivirine (RPV)
Protease inhibitors (PI)	inhibit the protease enzyme which is crucial for HIV replication	Atazanavir (ATZ), Darunavir (DRV), Fosamprenavir (FOS-APV), Lopinavir (LPV), Ritonavir (RTV), Saquinavir (SQV), Tipranavir (TPV)
Integrase strand transfer inhibitors (INSTI)	block the integration of HIV DNA into the host DNA	Bictegravir (BIC), Dolutegravir (DTG), Elvitegravir (EVG), Raltegravir (RAL)

Pre-treatment drug resistance

Pre-treatment drug resistance (PDR) can be defined as the resistant virus strains transmitted at the time of infection or acquired during previous exposure to ARVs. Resistance acquired during previous treatment can develop when a treatment had been interrupted or used for a short period of time as prophylaxis e.g Prevention of Mother to Child Transmissions, PrEP or intermittent anti-retroviral therapy [7].

PDR for commonly used first-line treatments, which include NNRTI, is increasing [8]. Because of this increase in the resistance to first line ART, it was recommended by the WHO to replace NNRTI as a first line regimen with a DTG (INSTI) based regimen [9]. According to WHO reports, the resistance to NNRTI is more common in people with previous exposure to ARV[7]. Moreover, in 70% of WHO survey reports, the PDR to NVP and EFV was above 10% [7]. The prevalence of NNRTI PDR in 2016 was estimated to be almost 10% in Africa, 9.4% in Latin America and the Caribbean, and 3.2% in Asia [10]. A systematic review conducted in West Africa and South Asia studied the prevalence of PDR and found out that PDR to NNRTI was 12%, to NRTI it was 12% and to PI it was 3% ([11]. INSTI drug resistance was very low in studies conducted in Cameroon and North Carolina [12,13].

ARVs are crucial in fighting the HIV epidemic and in reaching the SDG 3.3 goal, but ARV drug resistance can compromise the effectiveness of this measure. The increase of ARV drug resistance has a devastating impact on treatment outcomes and HIV infection prognosis as well as on the economy, since the second line treatments are 3 times more expensive and third line treatments are 18 times more expensive than first line treatments [14].

ARV medicine stock-outs are defined by the WHO as the complete absence of a medication for at least one day at storage delivery point. Stock-out is one of the early warning indicators of ARV drug resistance at clinic level surveyed by WHO. The interruption of drug supply is associated with increased risk of drug resistance, because it affect the patient supply and adherence to the regimen [15]. Poor Adherence to ARV has been associated with an increased risk in PDR [16].

Countries are classified according to gross national income (GNI) in to low, lower-middle, upper-middle, and high Income countries [17]. In low- and middle income countries the PDR

resistance is increasing in contrast to high income countries [18]. Human development index (HDI) is an indicator for health, income, and education which is a good estimator for the progress of human development. Life expectancy at birth is used to assess the health dimension. Education is evaluated by years of schooling and expected years of entering school for children. Income is measured by GNI [19]. HDI is an important factor to assess the socioeconomic status of a country [20].

National health expenditure (NHE) is an indicator for the health financing system, transparency, accountability, and monitoring of health resources in a country. Total health expenditures correspond to the amount spent on health care and related activities, including expenditures from both public and private funds [21]. Out of pocket health expenditure are the main source of health financing in low- and middle-income countries. Previous studies have shown that drug resistance was strongly correlated with out of pocket health expenditure [22].

Despite the importance of ARVs and the impact of PDR on combating HIV infection, only few studies have assessed the impact of socio-economic determinants (HDI and NHE), drug logistic determinants (stock-out), and patients determinants (adherence and previous exposure to any kind of ARV) on PDR.

Research objectives

The main aim of this thesis was to investigate the effect of the drivers on PDR, by assessing the effect of adherence, ARV, and ART previous exposure, HDI, NHE, stock-out, and PrEP on PDR. Also, the study aimed to investigate the differences in ARV-PDR prevalence between the regions Pacific, Asia, Eastern Mediterranean region, Africa, Latin America

Research question

What is the effect of the drivers (adherence, ARV, and ART previous exposure, HDI, NHE, stock-out, and PrEP) on PDR?

Method

This retrospective, cross-sectional observational study was conducted with literature data extracted from published, publicly available data bases and reports by international organizations. The positivistic approach was used as a framework where focus lies on assessing relationships between a dependent variable (ARV-PDR) and multiple independent variables. The independent variables studied were socioeconomic (HDI and NHE), patient (adherence, previous exposure to ARV and ART, and PrEP consumption) and logistics determinants (ARV stock-out). Table 2 shows the extracted data descriptions and sources.

Data preparation

PDR data, ARV previous exposure, and ART (ARV combination regimen) previous exposure variables were extracted from WHO report [23] (Table 2), the data was collected 2017-2020. PDR data for four different HIV drug categories (NNRTI, NRTI, PI, INSTI) was extracted at country level. ARV and ART were extracted as percentages from the HIV Drug Resistance Report 2021 by the WHO. The PDR was categorized by WHO in two groups: HIV drug resistance among treatment-naive ART initiators and HIV drug resistance among ART initiators. For the sake of this analysis, the two groups were combined to have one value of drug resistance for inferential analysis[23]. On-time pill pick-up (adherence), was extracted from the Global report on early warning indicators of HIV drug resistance by the WHO, the data was collected through a cross-sectional study conducted by the WHO [24] (Table 2). Drug stock outs were extracted from Global report on early warning indicators of HIV drug resistance by the WHO, the data was derived from pharmacy stock reports and measured the proportion of months with any anti-retroviral drug stock out [24] (Table 2). PrEP data was extracted from PrEPWatch as the number of individuals who received PrEP for at least one day [25] (Table 2). To calculate the proportion of PrEP consumers in each country, the number of PrEP users was divided by the total population in 2022 [18,27].

Table 2 PDR drivers' sources and description

Variable	Year(s) data was collected	Report title/ webpage	Organization or author	Year published
Pre-treatment drug resistance	2017-2020	HIV Drug Resistance Report 2021[23]	WHO	2021
Previous exposure to ART and ARV	2017-2020	HIV Drug Resistance Report 2021[23]	WHO	2021
Pre-exposure prophylaxis (Prep)	2022	The global PrEP tracker[25]	AVAC	2022
Human development index (HDI)	2019	Human Development Reports [19]	UNDP	2021
National health expenditure	2019	Global Health Expenditure Program [21]	UN	2021
Drug stock-outs	2005-2014	Global Report On Early Warning Indicators Of HIV Drug Resistance [24]	WHO	2016
ART adherence	2005-2014	Global Report On Early Warning Indicators Of HIV Drug Resistance [24]	WHO	2016

Regional drug resistance data

The PDR prevalence values in regional level (Pacific, Asia, Eastern Mediterranean region, Africa, Latin America) for the years 2004-2010 were extracted from WHO report (HIV drug resistance report 2012)[26]. The year 2014 data values were extracted from WHO report (HIV drug resistance report 2021). The PDR values were expressed as percentages [23] .

Statistical analysis

Inferential statistics were used to assess the drivers of PDR. To analyse possible drivers for PDR one linear regression model for each ARV class was used. PDR for ARV was used a response variable and previous exposure to ARV and ART, PrEP, NHE, HDI and stock-out of ARV were used as explanatory variables in a full model. The full model was reduced with backwards elimination using adjusted R^2 and p-values to find the simplest most informative model.

Mixed linear model was used to study the differences in PDR value on a regional level. In the model, ARV-PDR on regional level was used as a response variable. The region and years were explanatory variables for comparison of the regions for the same years. To compare the PDR within the same year, the year function was fixed in the model. An ANOVA test was performed to assess the significance of the mixed linear model. The statistical tests were performed in R [(27)] and RStudio [(28)] software to analyse the data.

Results

The PDR in 2021 to four different drug classes NRTI, NNRTI, PI, and INSTI was assessed on country level (figure 1). The results indicate the NNRTI-PDR was the most prevalent in those countries. Seven out of 29 countries had PDR to all four types of ARV drug classes, more than half of them are located in Latin America (Uruguay Argentina, Guatemala, El Salvador and Mexico), along with South Sudan and Ethiopia. Uruguay PDR prevalence was 110% for all four drug classes.

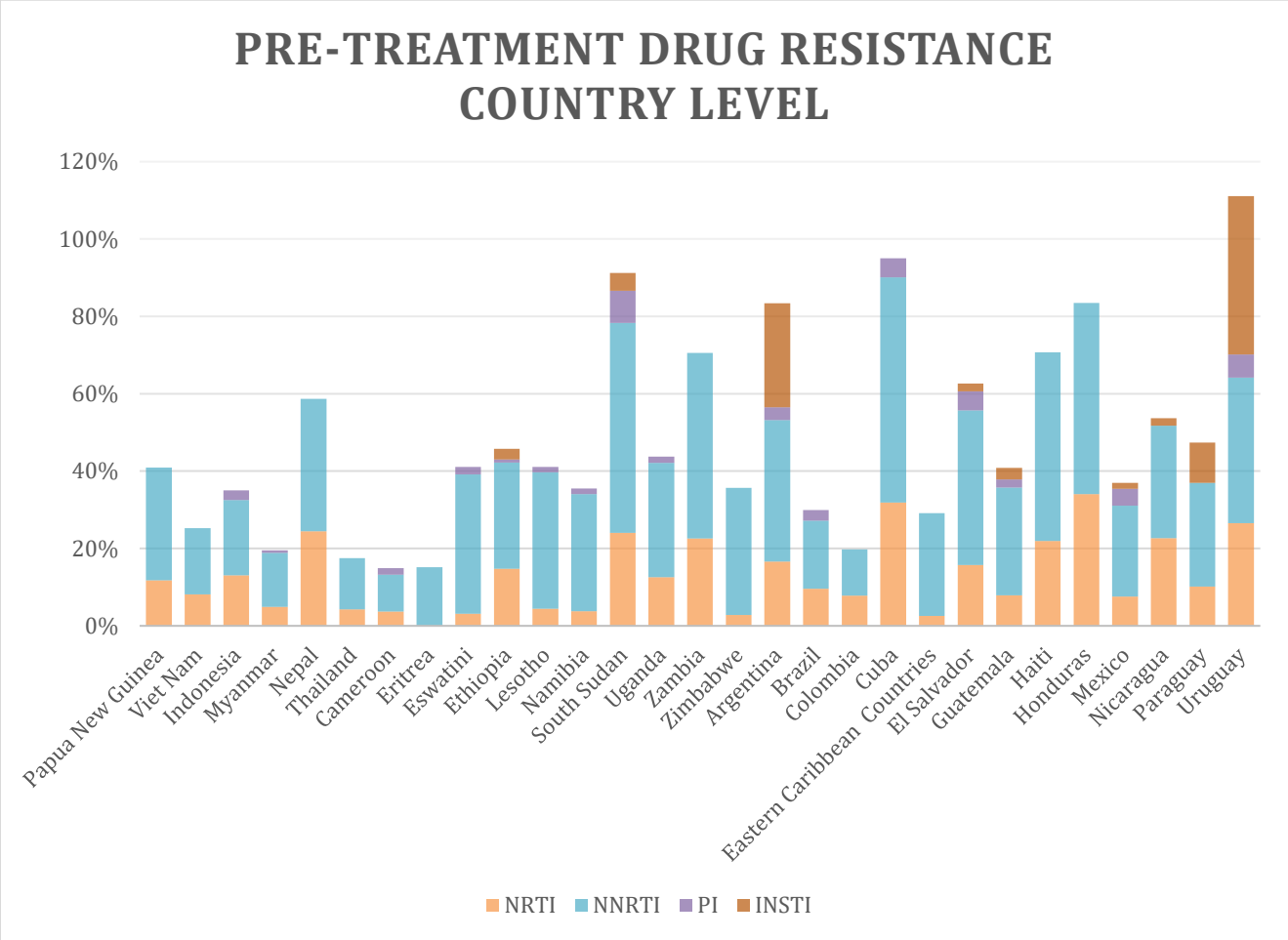

Figure 1 Prevalence of antiretroviral (NRTI,NNRTI,PI,INSTI) pre-treatment drug resistance on country level for 2021, based on WHO report [23]

Pretreatment drug resistance drivers

PDR of ARV was studied in 29 countries extracted from WHO report [23]. Linear regression model was used to assess the drivers' effect on ARV-PDR. One linear model for each ARV class was chosen according to the adjusted R^2 value and p value. ARV-PDR for each drug class (NRTI, NNRTI, PI and INSTI) served as a response variable. The previous exposure to ARV and ART, PrEP, NHE, HDI and stock-out of ARV were used as explanatory variables.

ARV previous exposure increases the PDR to NRTI ($p<0.01$). Table 3 shows that there was 0.15% (±0.05) increase in NRTI-PDR with every percentile increase in ARV previous exposure. PrEP consumption was not associated with the PDR of NRTI ($p>0.05$) (table 3). Other drivers (Adherence, ART previous exposure, HDI, NHE, Stock-out) were removed from the model since they did not contribute to the understanding of the model.

NNRTI-PDR value was statistically significant associated with previous exposure to ARV and PrEP consumption ($p<0.01$). The previous exposure to ARV increases the NNRTI-PDR by 1.41% (±0.34) for every percentile increase in ARV previous exposure. The effect of PrEP consumption on NNRTI-PDR was small with an estimate almost zero (0.0000*17%)* with p value *0.01.* The previous exposure to ARV combination therapy (ART) decreased the NNRTI-PDR by 0.16% (±0.59) for every percentile increase in ART previous exposure ($p=0.051$). It was no statistically significant association with NNRTI-PDR and the ARV stock out (table 3)

HDI was statistically significant with an increase the PI-PDR ($p<0.05$). A 1% increase in HDI result an increase of 0.06% (±0.03) in the PI-PDR. While the previous exposure to ART and PrEP consumption was not associated the PI-PDR (table 3). The rest of the drivers (adherence, ARV previous exposure, HDI, NHE and PrEP proportion) did not contribute to the understanding of PI-PDR.

Table 3 Showing that INSTI-PDR is associated with HDI ($p<0.001$). A 1% increase in HDI contribute with an increase in INSTI-PDR with 0.47% (±0.03). The only variable included in the model with HDI is ARV previous exposure, the rest of the drivers did not contribute to the model understanding.

Table 3 The estimated effect (%) of ART previous exposure, ARV previous exposure, HDI, NHE, PrEP consumption, PrEP proportion and stock-out on PDR of ARV drug classes (NRTI,NNRTI, INSTI, and PI). Significant effects are in bold

Drug Class	*ART previous exposure*	*ARV previous exposure*	*HDI*	*NHE*	*PrEP consumption*	*PrEP proportion*	*stock-out*
NRTI	-	**0.158****	-	-	2.877 e-07	-2.070	-
NNRTI	-0.16[#]	**1.41****	-	-	1.70E-06	-	-0.42
INSTI	-	0.001	**0.47*****	-	-	-	-
PI	-5.01e-05	-	**0.06***	-	6.86e-09	-	-

*ρ<0.05, **ρ<0.01, ***ρ<0.001, # p=.05

Regional drug resistance

Nucleoside reverse transcriptase inhibitor (NRTI)

There was no significant difference of NRTI PDR prevalence between the regions (Pacific, Asia, Eastern Mediterranean region, Africa, Latin America) and PDR prevalence remained the same between 2004-2014 (*p* value > 0.05) (Table 4 and Figure 2).

Table 4 ANOVA for coefficients from a linear mixed model analysing NRTI pre-treatment drug resistance prevalence among the Pacific, Asia, Eastern Mediterranean region, Africa, and Latin America from 2004-2014

	Chi^2	DF	P
Region	10.064	6	0.122
Year	0.001	1	0.971

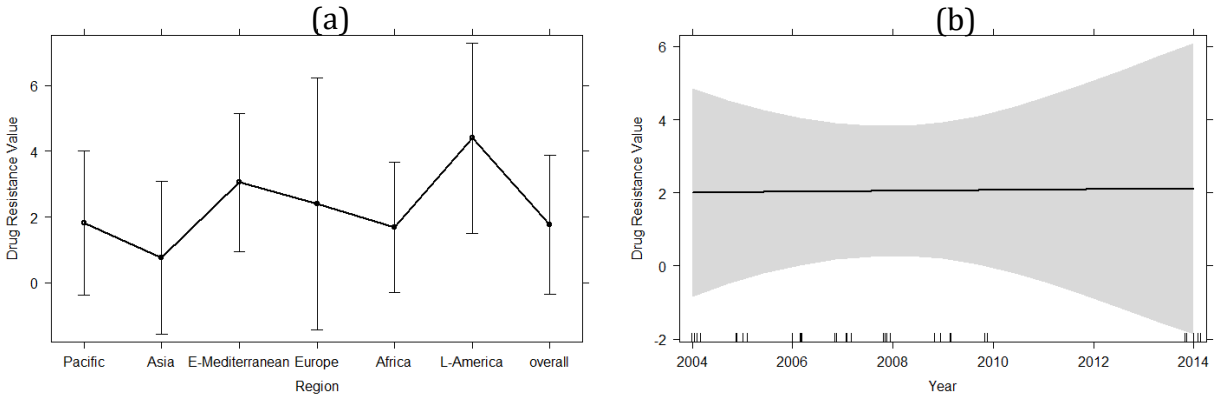

Figure 2 (a) Drug resistance for NRTI PDR prevalence in Pacific, Asia, Eastern Mediterranean region, Africa, Latin America). Error bars denote 95%CI, (b) Drug resistance for NRTI pre-treatment Pacific, Asia, Eastern Mediterranean region, Africa, Latin America from 2004-2014 (ANOVA; linear mixed model; p < 0.001)

Non-nucleoside reverse transcriptase inhibitor (NNRTI)

There were no statistically significant differences in the mean NNRTI PDR prevalence between Pacific, Asia, Eastern Mediterranean region, Africa, Latin America, ($p>0.05$). But there was an annual increasing trend of NNRTI PDR prevalence (2004-2014) ($p < 0.001$), (Table 5 and Figure 3).

Table 5 ANOVA for coefficients from a linear mixed model analysing NNRTI pre-treatment drug resistance prevalence among the Pacific, Asia, Eastern Mediterranean region, Africa, and Latin America from 2004-2014

	Chi^2	DF	P
Region	8.07	6	0.23
Year	29.19	1	**<0.001**

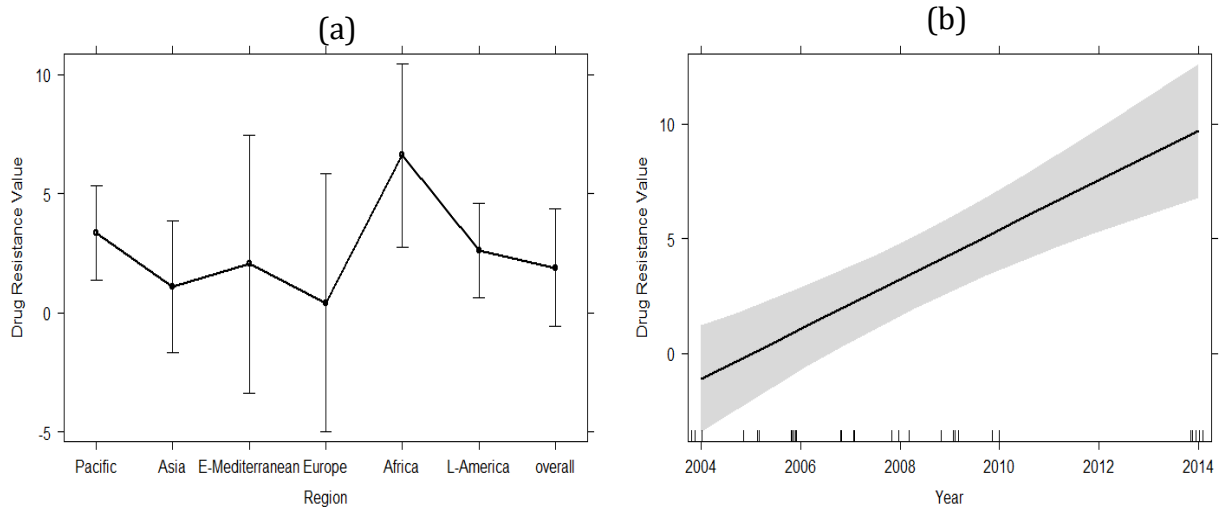

Figure 3 (a) Drug resistance for NNRTI PDR prevalence in Pacific, Asia, Eastern Mediterranean region, Africa, Latin America). Error bars denote 95%CI. (b) Drug resistance for NNRTI pre-treatment Pacific, Asia, Eastern Mediterranean region, Africa, Latin America from 2004-2014 (ANOVA; linear mixed model; $p < 0.001$).

Protease inhibitor (PI)

There were no differences among Pacific, Asia, Eastern Mediterranean region, Africa, Latin America in the PI PDR value (p value > 0.05). There was no statistically significant trend over time (p>0.05) (Table 6 and Figure 4).

Table 6 ANOVA for coefficients from a linear mixed model analysing PI pre-treatment drug resistance prevalence among the Pacific, Asia, Eastern Mediterranean region, Africa, and Latin America from 2004-2014

	Chi^2	DF	P
Region	3.6751	6	0.7205
Year	1.2249	1	0.2684

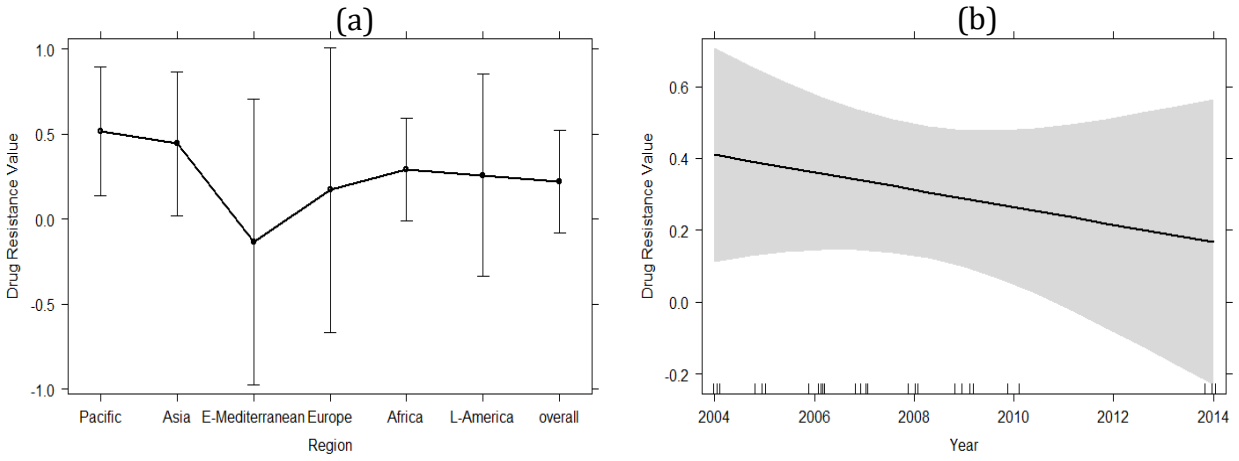

Figure 4 Drug resistance for PI PDR prevalence in Pacific, Asia, Eastern Mediterranean region, Africa, Latin America). Error bars denote 95%CI. (b) Drug resistance for PI pre-treatment Pacific, Asia, Eastern Mediterranean region, Africa, Latin America from 2004-2014 (ANOVA; linear mixed model; p > 0.05).

There was no regional data for Integrase strand transfer inhibitor (INSTI) available and therefore regional PDR could not be assessed.

Discussion

This study assessed the impact of socio-economic determinants (HDI and NHE), drug logistic determinants (stock-out), and patient determinants (adherence and previous exposure to any kind of ARV) on PDR.

The study showed that NNRTI-PDR was the most prevalent PDR. The average prevalence of NNRTI-PDR among the 29 countries studied was 30%. This can be explained by the fact that NNRTI has low genetic barrier to resistance, which means a single mutation of HIV can result in drug resistance, while PI and INSTI have high genetic barriers, with relatively low rates of PDR of 2% and 3%, respectively [28,29]. Similar to the results in this study, the PDR of NNRTI was the most prevalent among ARV classes in a studies conducted in China, West Africa and South Asia [12,30].

Seven out of 29 countries assessed in this study have PDR to NRTI, NNRTI, INSTI, and PI. More than half of these countries are located in Latin America (Uruguay, Argentina, Guatemala, El Salvador and Mexico), two are located in Africa (South Sudan and Ethiopia) (figure 1). In Uruguay, the total drug resistance was 110%. The reason behind this interesting result might be the fact that patients may encounter more than one resistant HIV strain and interclass resistance [31]. The drug class with the highest level of PDR in Uruguay was INSTI with 41%. The result interestingly contradicts the results by Scutari et al., who indicated that INSTI drug resistance occurs very rarely in drug naïve individuals [32]. However, the study at hand didn't differentiate between drug naïve individuals and individuals re-initiating ART or individuals previously exposed to ARV, which might explain the difference in the result. Moreover, according to the linear regression model (Table 3), INSTI was associated with HDI; the higher the HDI the higher the INSTI PDR, and Uruguay has a high HDI (0.81).

HDI was a significant determinant in the PDR for PI and INSTI, meaning that a higher HDI associated with higher levels of PDR. A reason for this could be that PI and INSTI are more expensive than NRTI and NNRTI [33], and this probably means they are more readily available in countries with higher HDI. Due to the increase in the resistance to NNRTI, the WHO has recently recommended the use of INSTI as a component of first-line ART regimens [34]. However, before the WHO changed the recommendations both the PI and INSTI were used only by high income countries [29]. In order to facilitate access to ARV for middle- and low-income

countries, the Medicine Patent Pool in agreement with pharmaceutical companies lowered the price for ARV[34].

Previous exposure to ARV, drug stock-out and national health expenditure did not significantly affect the prevalence of PDR for PI and INSTI. INSTIs are relatively new class; for example Dolutegravir was approved in 2013 [35]. NRTI and NNRTI PDR prevalence was affected by the previous exposure to ARVs. This finding was consistent with a systematic review that found that the risk of drug resistance was three times higher in previously exposed individuals compared to drug naïve individuals in low- and middle-income countries [11]. The analysis showed that NNRTI PDR increased with the increase in PrEP consumption. The PrEP regimen uses Tenofovir disoproxil fumarate and Emtricitabine combination which are NRTI classified. This was also shown by Shulman et al., who demonstrated the cross-resistance between NRTI and NNRTI [31]. Table 3 showed the protective effect of drug combination (ART previous exposure) against NNRTI-PDR. Meaning the use of drug combination negatively affect the NNRTI-PDR [36]. PrEP consists of combined therapy but belongs to the same ARV drug class as NRTI, while ART contain NRTI combined with other classes. According to the result of this analysis, use of drug combinations from different classes can decrease the PDR of NNRTI. Study by Wallis et al., emphasized the importance of viral load monitoring by following the use of drug combination to emphasize the effectiveness of the combination in fighting the virus[37]. The effect in other classes was not significant in this study but we cannot exclude its effectiveness there as well.

The data points for adherence data were insufficient to run a statistical analysis. Therefore, adherence was eliminated from each model. As shown in previous studies poor adherence to the drug regimen may increase the chance of resistance to ARV[37]. NHE was not significant in any of the model this might be because most of the country studied were Low- middle income countries where they counted mainly to out-of pocket health expenditure which was found to be related to drug resistance [20].

Adopting the new guideline in replacing the NNRTI with INSTI in countries where resistance is abundant is a good strategy in fighting the resistance and enhancing the quality of lives. But still the question needs to be answered with the persistence of drug resistance and the impact of Covid-19 on the logistics, if the SDG 3.3 goal can be achieved by 2030.

Conclusion

PDR is a major issue to public health globally. Many factors can affect the development of drug resistance. This study focused on different factors that drives the resistance (adherence, previous exposure to ARV and ART, HDI, NHE, PrEP consumption, stock-out). The use of drug combinations has beneficiary effects in reducing the resistance. Using ARV for a short period of time was associated with increased PDR. There were no regional differences in PDR despite the fact that Africa contains more than 60% of patients infected with HIV[38]. To combat the rise of ARV resistance, ARV drug resistance surveillance should be enhanced, the accessibility to viral load testing should be improved, adherence to treatment should be improved, and the retention and the quality of ART programmes should be improved [12]. From this study we cannot exclude the effect of stock-out and adherence in the rise of PDR which need further study.

Limitation

The access to raw data was restricted by WHO to designated ministry of health and ART programme users. The data was heterogenous, probably since it was extracted from different sources. Important determinants like the adherence to ART [12] could not be included in the analysis due to lack of data. For stock-out, another important driver of PDR, the data was old (starting in 2004-2010), inconsistent (the collection dates for countries were different), and incomplete (not all countries included in this analysis had data).

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Appendix

Pre-treatment ARV drug resistance, linear regression model coefficients.

Table 7 Linear regression model coefficient of NRTI-PDR prevalence

	Estimate	*Std. Error*	*t value*	*P [c]*
(Intercept)	*0.06*	*0.02*	*3.42*	*0.006*
PrEP proportion	*-2.07*	*1.21*	*-1.71*	*0.12*
ARV previous exposure [a]	*0.16*	*0.05*	*2.94*	***0.013***
PrEP [b]	*2.877 e*-07	2.326e-07	1.24	0.24

a ARV antiretroviral , b PrEP Pre=exposure prophylaxis, c p value is significant if it was less than 0.05, the confidence interval 95%.

Table 8 Linear regression model coefficient of NNRTI-PDR prevalence

	Estimate	*Std. Error*	*t value*	*P [c]*
Intercept	0.15	0.05	3.38	0.028
Stock Out	-0.42	0.19	-2.23	0.09
ARV previous exposure[a]	1.41	0.34	4.14	**0.01**
ART previous exposure	-0.16	0.059	-2.76	0.05
PrEP[b]	1.70E-06	3.98E-07	4.27	**0.01**

a ARV antiretroviral , b PrEP Pre=exposure prophylaxis, c p value is significant if it was less than 0.05, the confidence interval 95%.

Table 9 Linear regression model coefficient of PI-PDR prevalence

	Estimate	*Std. Error*	*t value*	*P [d]*
Intercept	-0.02	0.02	-1.23	0.24
HDI[a]	0.06	0.03	2.22	**0.04**
ART previous exposure [b]	-5.01e-05	9.34e-05	-0.53	0.60
PrEP [c]	6.86e-09	5.82e-08	0.11	0.90

a HDI : Human development index, b ART antiretroviral Therapy, c PrEP Pre=exposure prophylaxis, d p value is significant if it was less than 0.05, the confidence interval 95%.

Table 10 Linear regression model coefficient of INSTI-PDR prevalence

	Estimate	*Std. Error*	*t value*	*P [c]*
Intercept	*-0.27*	*0.10*	*-2.57*	*0.01*
HDI[a]	*0.47*	*0.16*	*2.92*	***0.009***
ARV[b] previous exposure	*0.001*	*0.001*	*1.03*	*0.31*

a HDI : Human development index, b ARV antiretroviral, c p value is significant if it was less than 0.05, the confidence interval 95%.