**MSc BIOSTATISTICS**

NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

MEDICAL SCHOOL

MATHEMATICS DEPARTMENT

# Multimorbidity in People living with HIV: prevalence, risk factors and trends.

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01

# Introduction

# HIV

Epidemiological insights of HIV infection

# Epidemiological characteristics

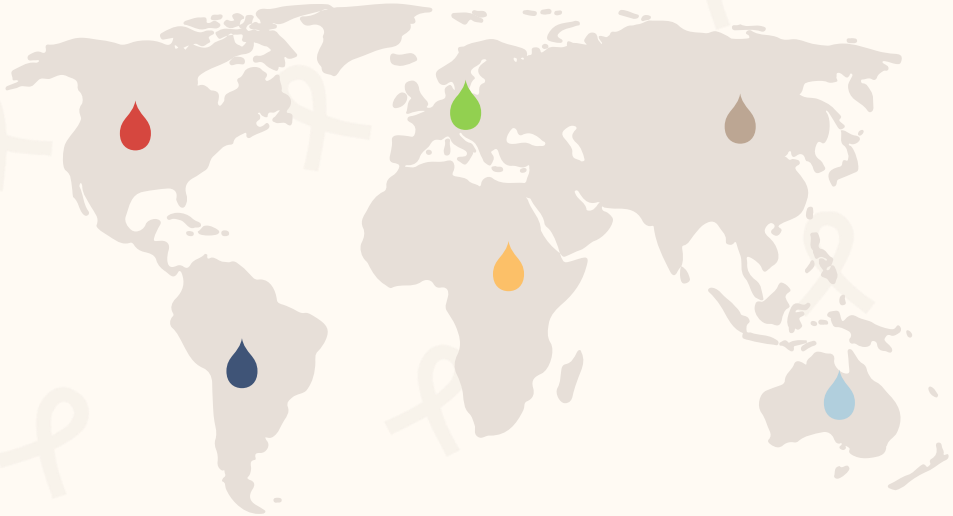


- 76 million people have been infected with HIV to date while 33 million have died.

**2019**

- 38 million.[31,6-44,5] people live with HIV.
- 1,7 million new infections.
- *0,7% [0,6-0,9%] 5-49 aged population lives with HIV.*
- *0.67 million died .*

# Prevalence



### AFRICA

Sub-Saharian: 4,9%,
North Africa and
Middle East: 0,2%

### North America

0,6%

### South America

0,4%
Caribbean 1,0%

### ASIA

East: 0,1%
South, South-East: 0,3%

### Oceania

0,3%

### EUROPE

West and Central: 0,2%
East and Central Asia: 1,0%

- 18710 total incidents until 09/03/2021.
- 82,5% Men – 17,3% Women.
- 4418 diagnoses of AIDS.

## 2020

- 601 new incidents.
- 482(80,2%) concerning men.
- 100 new AIDS infections.
- Στο 41% MSM transmitted .
- Στο 28% MSW transmited.
- Στο 11,9% IDU transmited.
- Ένα 18% unspecified.

# Antiretroviral therapy

cART : Combined Antiretroviral Therapy.

Availability : >1996

ART drugs categories:

- **Entry Fusion Integrase Inhibitors** : Entry Inhibitors
- **PIs** : Protease Inhibitors
- **INSTIs** : Integrase Inhibitors
- **NRTIs** : Nucleocide Reverse Transcriptase Inhibitors.
- **NNRTIs** :Non Nucleocide Reverse Transcriptase Inhibitors.

Today:

- HIV is considered as a chronic condition.
- cART has improved life expectancy and quality of life.
- Complications due to cART and natural aging.

# AIM

- Estimate of multimorbidity prevalence.
- Multimorbidity patterns.
- Investigation of changes over time.
- Investigation of risk factors.

02

# Multimorbidity

Definition

# Definition

- Multimorbidity: the coexistence≥2 diseases in the same individual.

- Assessment method: Patient history backround – counting the coexistence of diseases.

- Commonly accepted definition discrepancy - Data availability.

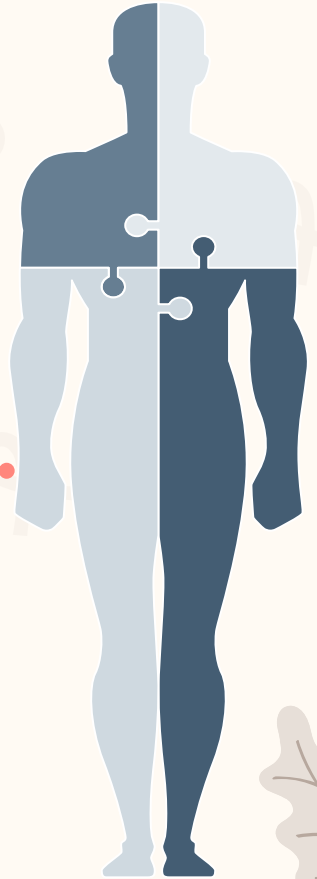
- At least 4 different diseases.

# Diseases Eligibility Criteria

- Diseases often treated by the primary and secondary health care.
- Diseases for which we had laboratory, pharmaceutical and diagnostic data to evaluate.
- Diseases that have been shown to have a higher incidence of HIV.
- Finally, diseases included in other studies on Multiple Disease and HIV.

# Diseases

- Diabetes Melitus
- Hypertension
- Dyslipidemia
- Renal disease
- Cardiovascular Disease
- Liver disease
- Malignancies



**Diabetes Melitus:** glucose measurements ≥126 mg/dl or glycosylated hemoglobin ≥6.5%.

**Hypertension :** systolic blood pressure ≥140 mmHG or diastolic pressure ≥90 mmHG.

**Dyslipidemia :** total cholesterol ≥240 mg/dL or the HDL cholesterol ≤ 35 mg/dL or triglycerides ≤200 mg/dL.

**CVD :** Coronary heart disease, Myocardial infarction, Stroke.

**Renal Disease:** through the estimated glomerular filtration rate(eGFR) throught CKD-epi formula. Individuals with EGFR<60 ml/min/1.73m² are considered as people with Renal disease.

**Liver Disease :** Chronic liver disease or cirrhosis.

**Malignancies** : all non-AIDS related malignancies.

03

# Data Source AMACS

- AMACS - Athens Multicenter AIDS cohort study

  - HIV people alive at 01/01/1996 – date of commencement of combined antiretroviral therapy.
  - The12 HIV-1 largest clinics in Athens and some regional.
  - Date collection: Antiretroviral therapy, Measurements of CD4, CI and viral load levels, results of other tests (hematological, urologic biochemical, serological), Death (causes of death), detailed recordi of infections, treatments other than antiretroviral, comorbidities anc other conditions.

  - Aim: To investigate possible long-term trends in Greece, in the natural history of HIV infection at the time of combined antiretroviral therapy.

# Study Design

Longitudinal Analysis

Eligibility Criteria:

- People aged ≥18 at the date of diagnosis of HIV infection.
- Start date of ART ≥01 / 01/1996.
- Exclude invalid dates of birth, HIV diagnosis and cART initiation.
- Exclude people at the time they died or were dropped out.

Creating a final sample: Repeating the selection criteria 19 times, from 2000 to 2018, limiting for each year our sample for observations until 31/12.

# Data

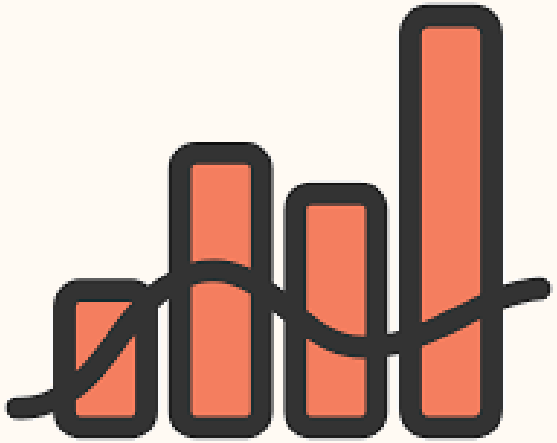
Variable of interest(**outcome**) : Multimorbidity (0=No ,1=Yes)

**Variables constant over time :**

- Gender (reference category: Female).
- Age at diagnosis in years (<40, 40-50, 50-60, 60+).
- Age of onset of ART (continuous in years) and categorical (<40, 40-50, 50-60, 60+).
- Method of transmission (MSM: men having sex with men, IDU: intravenous drug users, MSW: men having sex with women, Unknown / other).
- CD4 (cells / μl) measurement at diagnosis (<200, 200–349,350–499,500 +).
- CD4 (cells / μl) measurement at the start of ART (<200, 200–349,350–499,500 +).
- Race (White-Colored or other).
- Duration of antiretroviral therapy.
- The level of education (primary, secondary, tertiary, unknown).
- BMI body mass index (underweight, normal, overweight, obese).
- Region of origin (Europe, Africa, Asia, unknown

**Variables that change over time :**

- Current Age calculated at the beginning of each year (<40, 40-50, 50-60, 60+).
- Annual median CD4 cell count.
- Annual viral repression status (suppressed viral load for HIV RNA ≤400 copies / mL).
- ART use was defined as the regimen prescribed for most of the year, and we split it based on PI (dual PI / NNRTI, PI-based or PI-boosted regimens) into NNRTI-based, INSTIs (Integrase Strand Transfer Inhibitors) in No cART (people taking antiretrovirals but not a combined regimen) and No ART (for people not receiving treatment).
- Development of clinical AIDS (1 Yes- 0 No).



04

# Methods

## GEE

# Modeling

**Use of Generalized estimating equations(GEE)**

- GLM extension for longitudinal data.
- Marginal model.
- Well defined structure of the instrument.
- No distribution case.
- Semi-parametric model.
- Quasi-likelihood.
- Definition of correlation of repeated measurements within the individual.

# Model structure

- $g(\mu_{ij}) = \eta_{ij} = \boldsymbol{X}_{ij}\boldsymbol{\beta}$

Mean Response

Link function
(logit-Binary, log-count)

Linear estimator

- $\text{Var}(Y_{ij}) = \varphi \cdot \upsilon(\mu_{ij})$, Variance between individuals.

Scale Parameter
(under estimation or not)

Known variance function

- Per pair correlation within individuals : $\text{Corr}(Y_{ij}, Y_{ik}) = a_{jk}$

  $V_i = A^{1/2}{}_i \text{Corr}(Y_i) A^{1/2}{}_i$ → Working covariance matrix

- Sandwich Εκτιμητής

  It is used to estimate the SE of the parameters when the model we defined is not correct.
  -Robustness.

# Correlation structures

Πιο συχνά χρησιμοποιούμενες δομές συσχέτισης στα GEE.

| Correlation structure | $Corr(Y_{ij}, Y_{ik})$ | Sample matrix |
|---|---|---|
| Independent | $Corr(Y_{ij}, Y_{ik}) = \begin{cases} 1 & j = k \\ 0 & j \neq k \end{cases}$ | $R(\alpha) = \begin{pmatrix} 1 & 0 & \cdots & 0 \\ 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 1 \end{pmatrix}$ |
| Exchangeable | $Corr(Y_{ij}, Y_{ik}) = \begin{cases} 1 & j = k \\ \alpha & j \neq k \end{cases}$ | $R(\alpha) = \begin{pmatrix} 1 & \alpha & \cdots & \alpha \\ \alpha & 1 & \cdots & \alpha \\ \vdots & \vdots & \ddots & \vdots \\ \alpha & \alpha & \cdots & 1 \end{pmatrix}$ |
| Auto-regressive AR(1) | $Corr(Y_{ij}, Y_{ik}) = \alpha^{\lvert j-k \rvert}$ for $j=1,\ldots,n_i$ | $R(\alpha) = \begin{pmatrix} 1 & \alpha & \cdots & \alpha^{n_i-1} \\ \alpha & 1 & \cdots & \alpha^{n_i-2} \\ \vdots & \vdots & \ddots & \vdots \\ \alpha^{n_i-1} & \alpha^{n_i-2} & \cdots & 1 \end{pmatrix}$ |
| Unstructured | $Corr(Y_{ij}, Y_{ik}) = \begin{cases} 1 & j = k \\ \alpha_{jk} & j \neq k \end{cases}$ | $R(\alpha) = \begin{pmatrix} 1 & \alpha_{12} & \cdots & \alpha_{1n_i} \\ \alpha_{12} & 1 & \cdots & \alpha_{2n_i} \\ \vdots & \vdots & \ddots & \vdots \\ \alpha_{1n_i} & \alpha_{2n_i} & \cdots & 1 \end{pmatrix}$ |

# QIC Criterion

- Criteria for selection and comparison of models.
- Quasi-likelihood based (Wedderburn, 1974; McCullagh, 1983).
- Information for selecting a correlation structure.
- Information for selecting a subset of participants.

$$\text{AIC} = -2LL + 2p$$

$$\text{QIC} = -2Q(\widehat{\mu}; I) + 2\text{trace}(\widehat{\Omega}_I^{-1}\widehat{V}_R)$$

$\widehat{\mu} = g^{-1}(x\widehat{\beta})$ and $g^{-1}()$ is the inverse link function.

$\widehat{\beta}$ coefficient estimates

$\widehat{V}_R$ robust variance estimator

$R$ general working covariance structure

$\widehat{\Omega}_I$ variance estimator under the assumption of an independence correlation structure.

# Model selection mechanism

1. Selection of an appropriate correlation structure under the complete model.

2. Selection of variables under the selected correlation structure.

- Decision criterion: Lower QIC values.

# Statistical Analysis

1. Multivariate Analysis.

- Poisson regression with robust variation and St.Error estimated via Sandwich estimator in binary result.
- It is an approach of the Log-Bionomial model.
- Use GEE to calculate within-subject correlation.
- Exchangeable correlation structure.

Pros

- Direct estimate of Prevalence Ratios.
- Avoiding overestimation of odds ratio through logistic regression.
- Avoid convergence problems in Log-binomial μοντέλο.
- Correct estimates when the prevalence is above 10%.

2. Univariate Analysis

- Age adjusted.
- Independent correlation structure.

3. Additional Analysis

- Limit the sample to BMI data.
- Application of the final model adjusting for BMI.

- Fitting of the final model for each individual disease.
- Understanding the Prevalence of Constituent Diseases of Multimorbidity.

05

# RESULTS

# Descriptives

- Median follow up time(IQR): 7,8 years (3,5-13)
- N=6594  (2105  Multimorbidity+)

# Descriptives

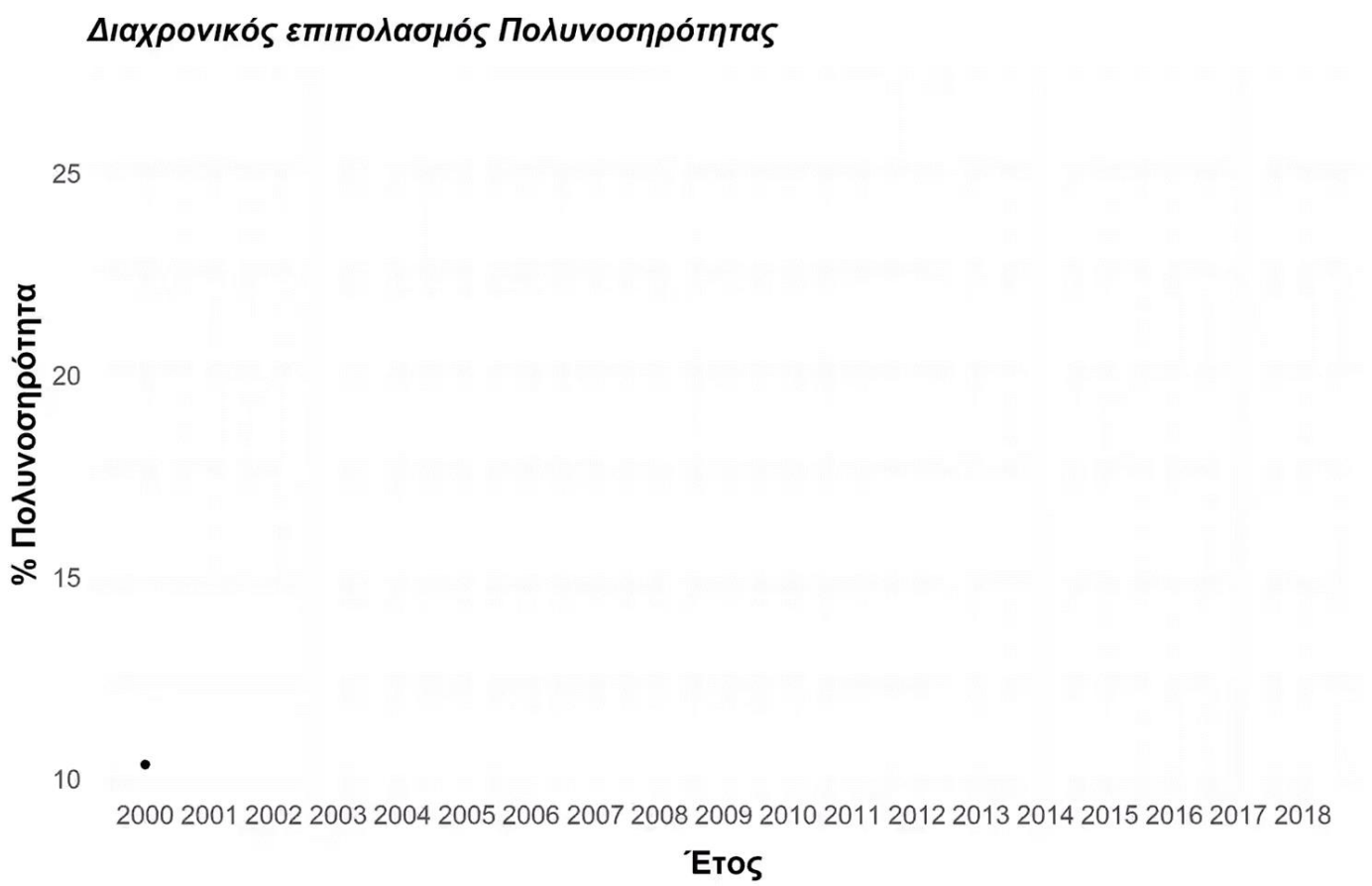
| | 2000<br>N=1032 | 2009<br>N=3397 | 2018<br>N=5562 |
|---|---|---|---|
| Median Age(IQR), years | 37(32-44) | | |
| Men% | 82.4% | | |
| Annual Median CD4 (IQR) cells/μl | 437(261-654) | | |
| Viral suppression% | 55.9% | | |
| Clinical AIDS % | 23.4% | | |

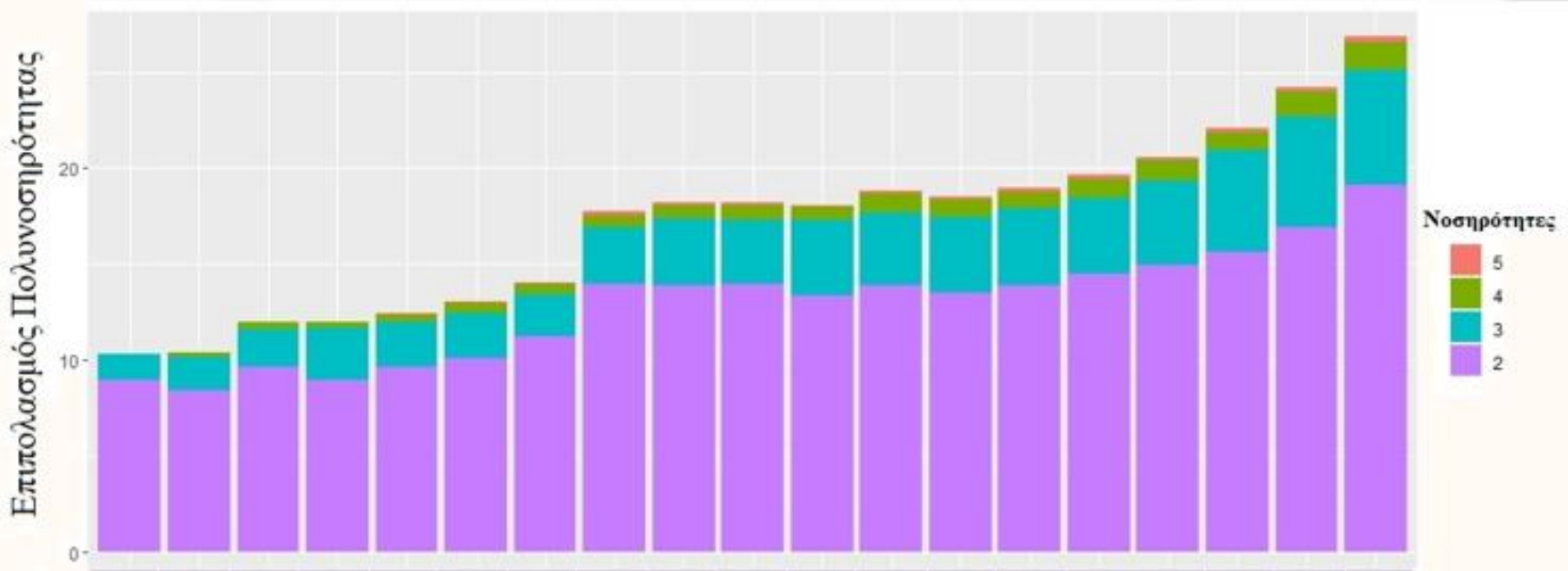
# Descriptives

| | 2000<br>N=1032 | 2009<br>N=3397 | 2018<br>N=5562 |
|---|---|---|---|
| Median Age(IQR), years | 37(32-44) | 41(35-49) | 46(38-54) |
| Men% | 82.4% | 83.8% | 86.5% |
| Annual Median CD4 (IQR) cells/μl | 437(261-654) | 521(362-716) | 676(480-885) |
| Viral suppression% | 55.9% | 72.3% | 89% |
| Clinical AIDS % | 23.4% | 19.1% | 14.3% |

| | 2000(N=1032) | 2009(N=3397) | 2018(N=5562) |
|---|---|---|---|
| **Transmission%** | - | - | - |
| **MSM** | 53.4% | 59% | 62.5% |
| **MSW** | 30.7% | 28% | 21% |
| **IDU** | 3.4% | 2% | 7.2% |
| **ART%** | - | - | - |
| **PIs** | 51.6% | 47.5% | 42.8% |
| **NNRTIs** | 16% | 28.3% | 33.3% |
| **INSTIs** | 0% | 0.45% | 20% |
| **No cART** | 17.8% | 4.5% | 1.7% |

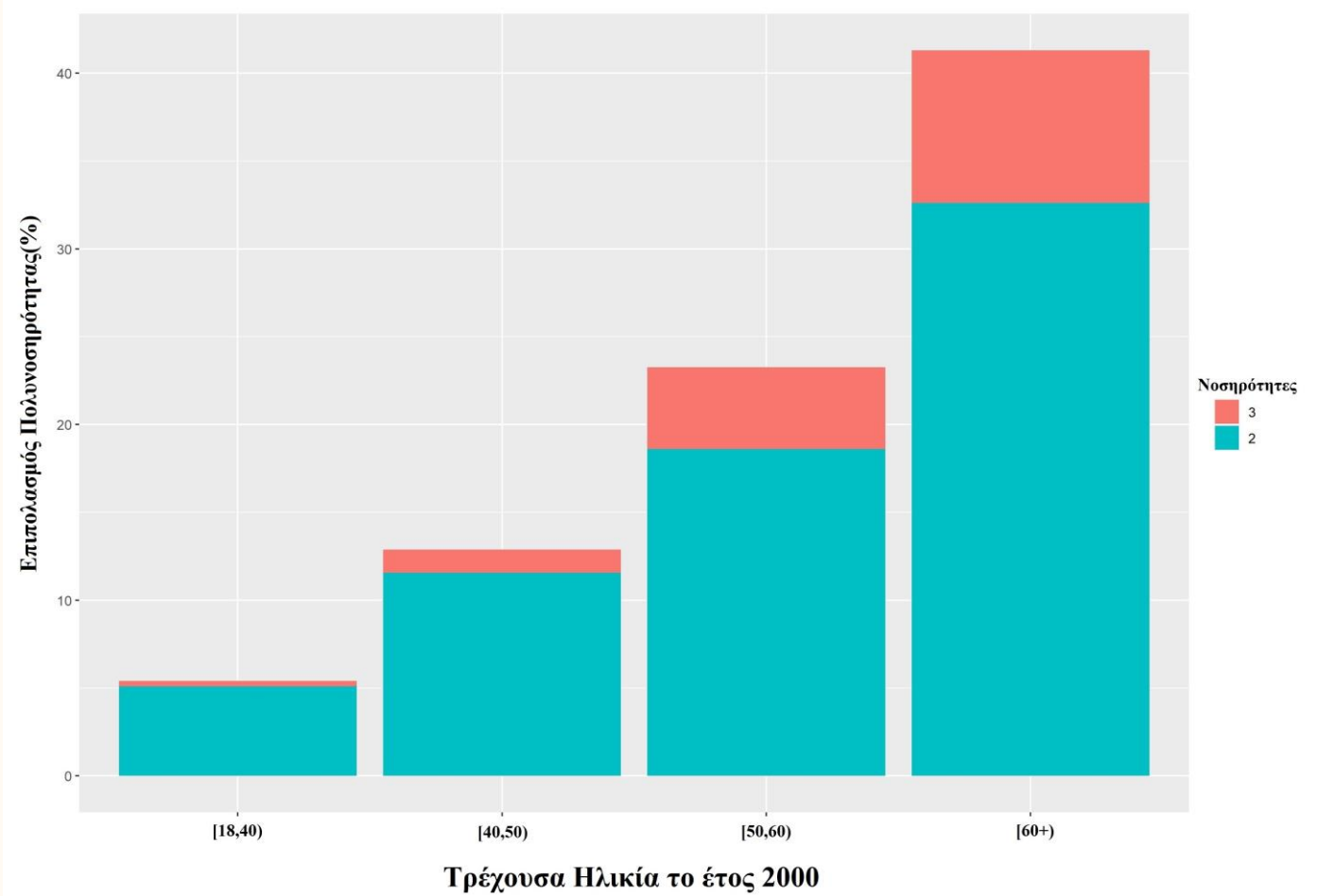
-Prevalence of multimorbidity through over the years.



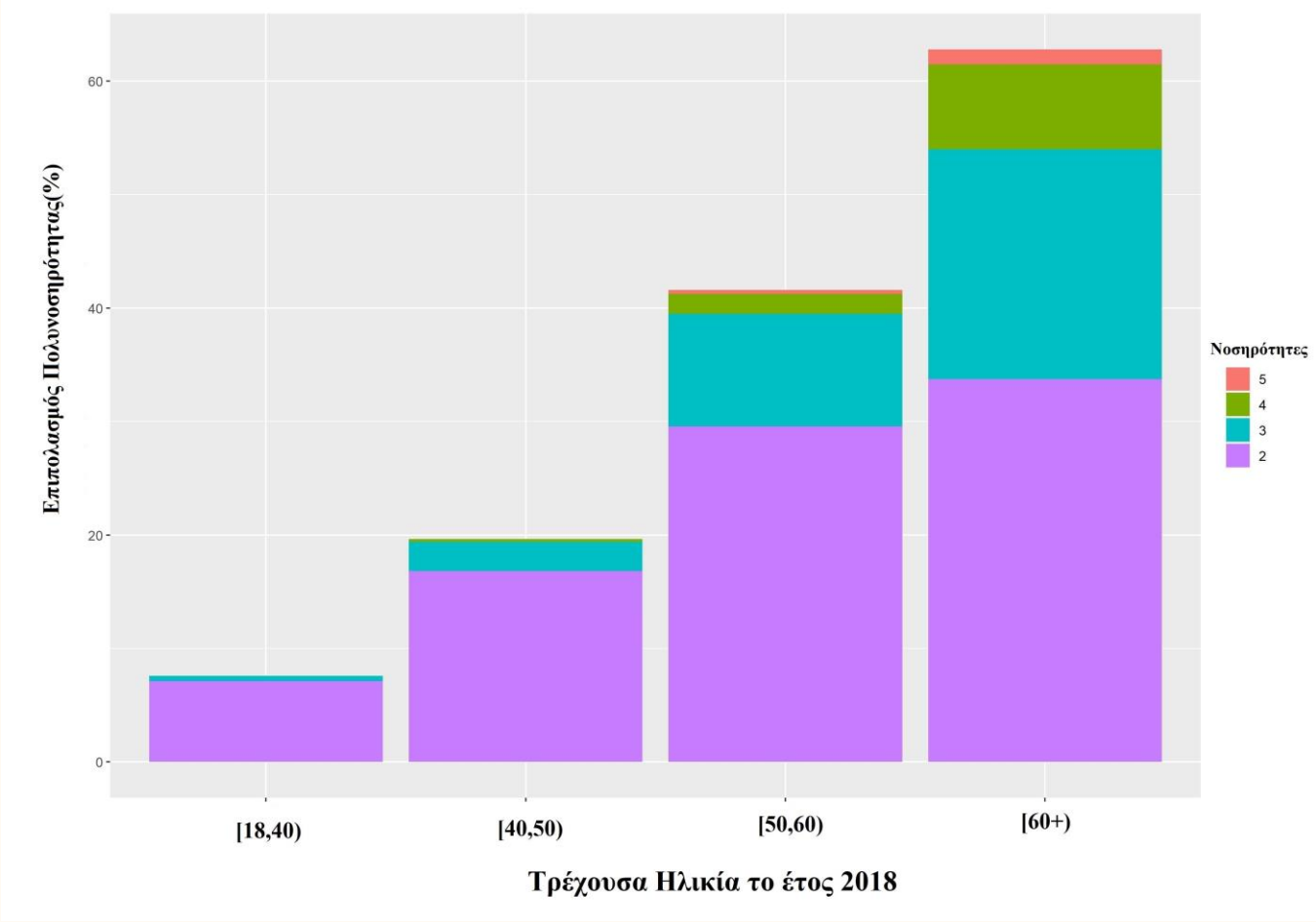



| # Νοσηροτήτων | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 88 | 96 | 126 | 131 | 163 | 194 | 243 | 338 | 378 | 459 | 466 | 521 | 542 | 587 | 626 | 672 | 722 | 798 | 892 |
| 3 | 13 | 20 | 25 | 40 | 40 | 45 | 48 | 72 | 95 | 110 | 139 | 142 | 159 | 171 | 172 | 196 | 246 | 272 | 280 |
| 4 | 0 | 2 | 5 | 4 | 7 | 10 | 11 | 16 | 19 | 25 | 23 | 37 | 36 | 36 | 42 | 47 | 40 | 62 | 69 |
| 5 | 0 | 0 | 0 | 0 | 1 | 2 | 2 | 5 | 4 | 4 | 4 | 6 | 8 | 10 | 11 | 10 | 13 | 9 | 12 |

# 2000

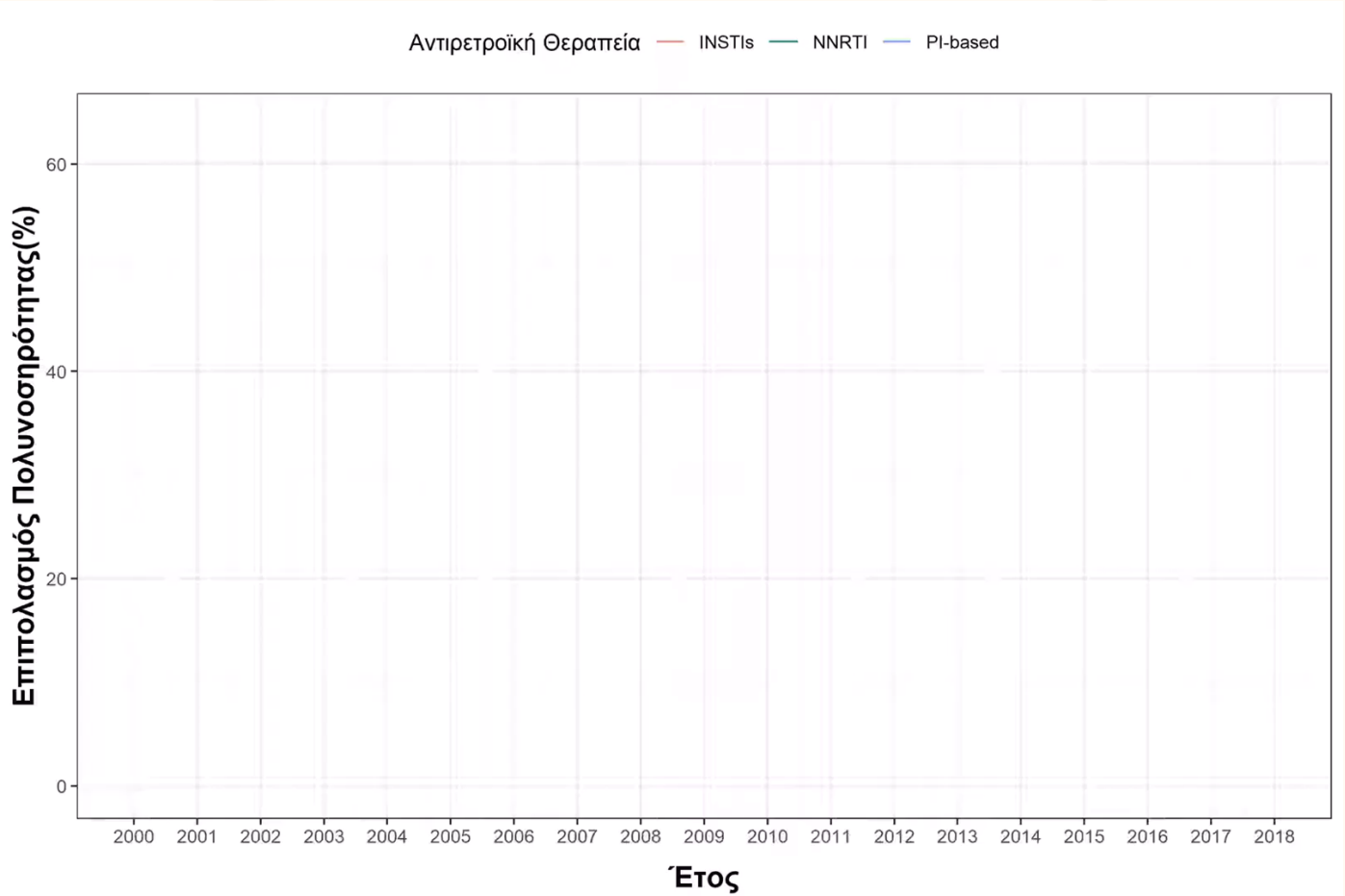

Επιπολασμός Πολυνοσηρότητας(%)
0
10
20
30
40
[18,40)
[40,50)
[50,60)
[60+)
Τρέχουσα Ηλικία το έτος 2000
Νοσηρότητες
3
2

# 2018


Επιπολασμός Πολυνοσηρότητας(%)
60
40
20
0
[18,40)
[40,50)
[50,60)
[60+)
Τρέχουσα Ηλικία το έτος 2018
Νοσηρότητες
5
4
3
2

- Prevalenve of Multmorbidity through over the years by current age goups.

- Prevalenve of Multmorbidity through over the years by current ART goups.



| | Death(N=522) 2000-2018 | Drop out(N=613) 2000-2018 |
|---|---|---|
| Multimorbidity % | 19 % | 7 % |
| 0 diseases % | 48.7 % | 70.3 % |
| 1 diseases % | 32.3 % | 22.7 % |
| 2 diseases % | 14.2 % | 5.34 % |
| 3 diseases % | 3.5 % | 1.47 % |
| 4 or 5 diseases % | 1.31 % | 0.18 % |

- 4299 Dyslipidemia+
- 1597 Renal disease+
- 899 Hypertension+
- 535 Diabetes+
- 266 CVD+
- 183 Malignacies+
- 36 Liver disease +

# Most frequent patterns

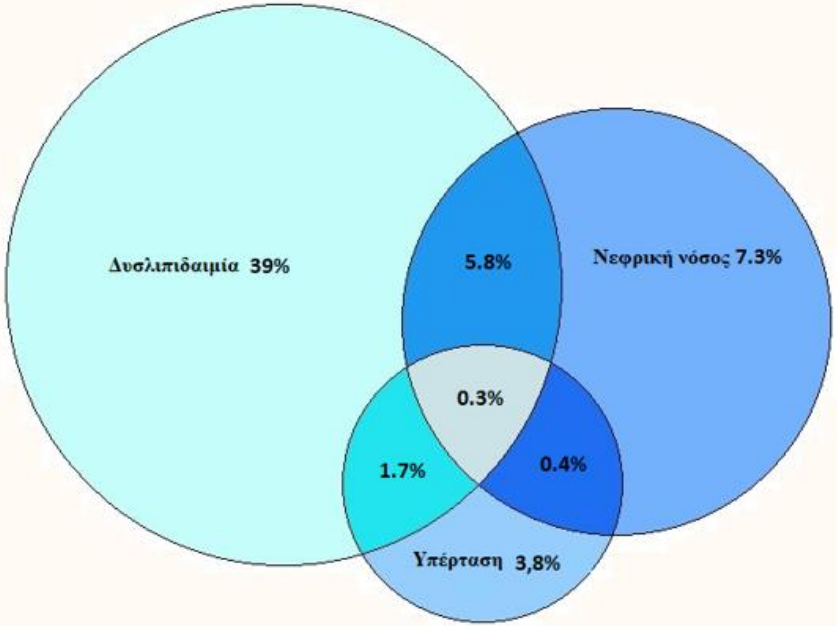
Dyslipidemia + Renal disease

Dyslipidemia + Hypertension

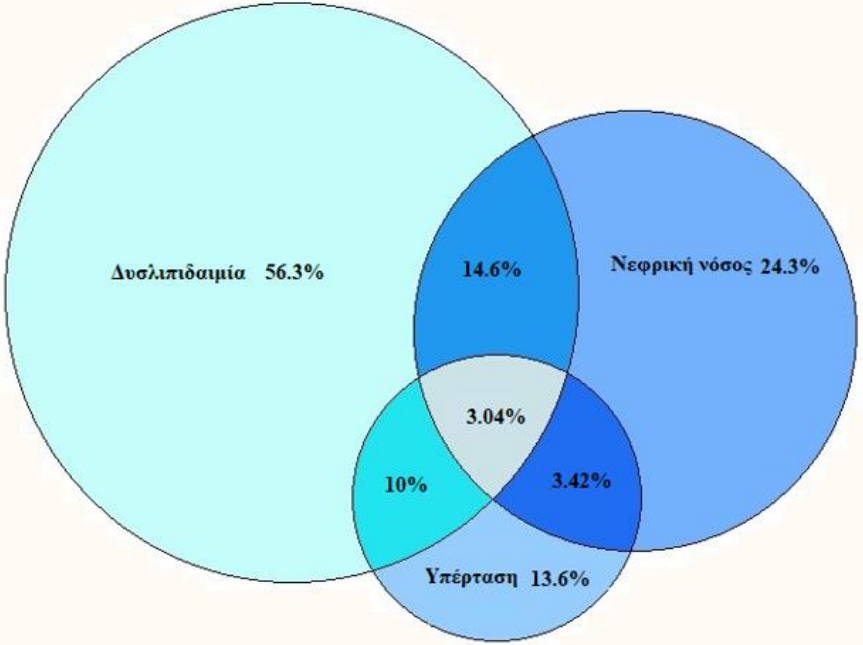
Hypertension + Renal disease

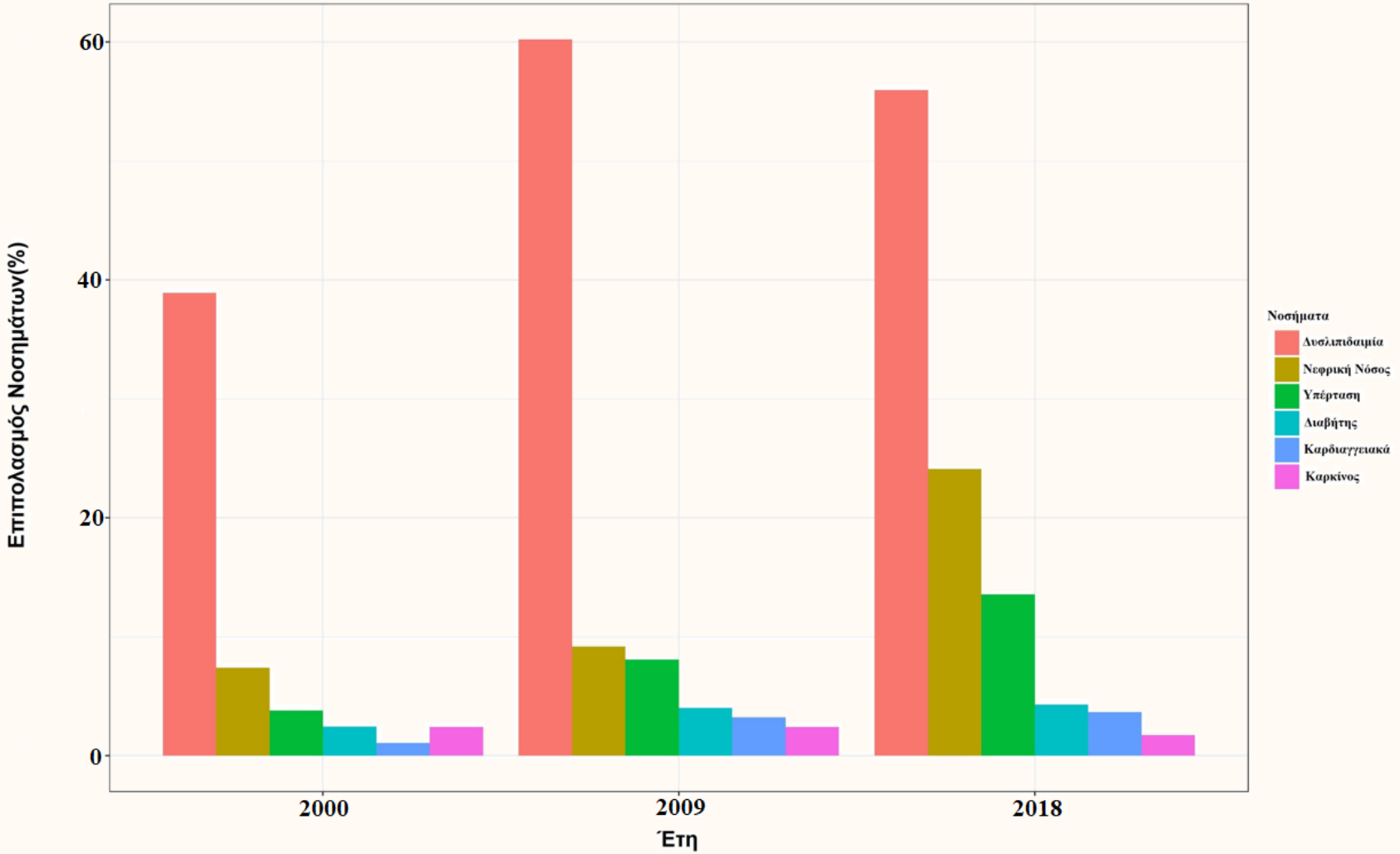
Dyslipidemia + Renal disease + Hypertension

# 2000


Δυσλιπιδαιμία 39%
5.8%
Νεφρική νόσος 7.3%
0.3%
1.7%
0.4%
Υπέρταση 3,8%

# 2018


Δυσλιπιδαιμία 56.3%
14.6%
Νεφρική νόσος 24.3%
3.04%
10%
3.42%
Υπέρταση 13.6%


Επιπολασμός Νοσημάτων(%)
60
40
20
0
2000
2009
2018
Έτη
Νοσήματα
Δυσλιπιδαιμία
Νεφρική Νόσος
Υπέρταση
Διαβήτης
Καρδιαγγειακά
Καρκίνος

| | Unadjusted αPR (95%C.I) | Adjusted PR* (95% C.I) N=45857, $N_{subject}$=5123 | +BMI (95% C.I) N=19862, $N_{subject}$=2327 |
|---|---|---|---|
| Age [40,50)vs.[18,40) (years) | **3.58** (3.20-4.02) | | |
| Age [50,60)vs.[18,40) (years) | **7.15** (6.30-8.12) | | |
| Age [60+)vs.[18,40) (years) | **11.47** (10.11-13.02) | | |
| Men vs. Women | **1.96** (1.47-2.02) | | |
| IDU vs. MSM | **0.54** (0.38-0.77) | | |
| Years 2013-2018 vs. 2000-2006 | **1.33** (1.2-1.48) | | |
| Annual CD4>500 vs. <200 (cells/μl) | **1.42** (1.3-1.56) | | |
| Viral suppression | **1.81** (1.65-1.99) | | |
| Diagnose of clinical AIDS | **1.19** (1.08-1.31) | | |
| Years since infection | **1.03** (1.02-1.04) | | |
| Receiving ART | **1.33** (1.18-1.51) | | |

[α] Adjusted for age. * Adjusted for age. , sex, race, Calendar year, transmission, AIDS diagnose, annual median CD4, CD4 at ART start, viral suppression , therapy, estimated time since infection.

| | Unadjusted αPR (95%C.I) | Adjusted PR* (95% C.I) N=45857, $N_{subject}$=5123 | +BMI (95% C.I) N=19862, $N_{subject}$=2327 |
|---|---|---|---|
| Age [40,50)vs.[18,40) (years) | **3.58** (3.20-4.02) | **1.82** (1.67-1.98) | |
| Age [50,60)vs.[18,40) (years) | **7.15** (6.30-8.12) | **2.51** (2.25-2.8) | |
| Age [60+)vs.[18,40) (years) | **11.47** (10.11-13.02) | **3.33** (2.92-3.79) | |
| Men vs. Women | **1.96** (1.47-2.02) | **1.92**(1.53-2.4) | |
| IDU vs. MSM | **0.54** (0.38-0.77) | **0.68** (0.50-0.94) | |
| Years 2013-2018 vs. 2000-2006 | **1.33** (1.2-1.48) | **1.39** (1.25-1.54) | |
| Annual CD4>500 vs. <200 (cells/μl) | **1.42** (1.3-1.56) | **1.08** (0.97-1.2) | |
| Viral suppression | **1.81** (1.65-1.99) | **1.41** (1.30-1.53) | |
| Diagnose of clinical AIDS | **1.19** (1.08-1.31) | **1.11** (0.97-1.27) | |
| Years since infection | **1.03** (1.02-1.04) | **1.036** (1.03-1.04) | |
| Receiving ART | **1.33** (1.18-1.51) | **1.17** (1.04-1.32) | |

[α] Adjusted for age. * Adjusted for age. , sex, race, Calendar year, transmission, AIDS diagnose, annual median CD4, CD4 at ART start, viral suppression , therapy, estimated time since infection.

| | Unadjusted αPR (95%C.I) | Adjusted PR* (95% C.I) N=45857, $N_{subject}$=5123 | +BMI (95% C.I) N=19862, $N_{subject}$=2327 |
|---|---|---|---|
| Age [40,50)vs.[18,40) (years) | **3.58** (3.20-4.02) | **1.82** (1.67-1.98) | **1.61** (1.41-1.83) |
| Age [50,60)vs.[18,40) (years) | **7.15** (6.30-8.12) | **2.51** (2.25-2.8) | **2.21** (1.87-2.62) |
| Age [60+)vs.[18,40) (years) | **11.47** (10.11-13.02) | **3.33** (2.92-3.79) | **2.76** (2.24-3.38) |
| Men vs. Women | **1.96** (1.47-2.02) | **1.92**(1.53-2.4) | **1.84** (1.32-2.56) |
| IDU vs. MSM | **0.54** (0.38-0.77) | **0.68** (0.50-0.94) | **0.63** (0.40-0.99) |
| Years 2013-2018 vs. 2000-2006 | **1.33** (1.2-1.48) | **1.39** (1.25-1.54) | **1.42** (1.18-1.71) |
| Annual CD4>500 vs. <200 (cells/μl) | **1.42** (1.3-1.56) | **1.08** (0.97-1.2) | **1.07** (0.96-1.20) |
| Viral suppression | **1.81** (1.65-1.99) | **1.41** (1.30-1.53) | **1.44** (1.32-1.57) |
| Diagnose of clinical AIDS | **1.19** (1.08-1.31) | **1.11** (0.97-1.27) | **1.20** (0.96-1.51) |
| Years since infection | **1.03** (1.02-1.04) | **1.036** (1.03-1.04) | **1.04** (1.02-1.05) |
| Receiving ART | **1.33** (1.18-1.51) | **1.17** (1.04-1.32) | **1.05** (0.88-1.26) |

[α] Adjusted for age. * Adjusted for age. , sex, race, Calendar year, transmission, AIDS diagnose, annual median CD4, CD4 at ART start, viral suppression , therapy, estimated time since infection.

| | **Underweight**<br>**BMI <20**<br>**weight/(height)$^2$** | **Overweight**<br>**BMI [25,30)**<br>**weight/(height)$^2$** | **Obese**<br>**BMI ≥30**<br>**weight/(height)$^2$** |
|---|---|---|---|
| **Prevalence Ratio(95% C.I) Vs. Normal BMI[20,25)** | **07** (0.48-1.04) | **1.40** (1.16-1.68) | **1.70** (1.32-2.19) |


Επιπολασμός Πολυνοσηρότητας(%)
0
10
20
30
40
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Έτος
BMI
Λιποβαρής
Κανονικός
Υπέρβαρος
Παχύσαρκος

# Conclusions

06

- The prevalence of polio is constantly increasing. Recent years have been associated with a higher prevalence.
- Older ages, transmission through sexual intercourse between men, men, viral repression status, cART intake, and time from estimated infection were associated with a higher risk for polyneuropathy.
- Dyslipidemia, Hypertension and Kidney Disease are the three most common diseases that lead to Multiple Disease.
- 4th most common is Diabetes.
- It has been estimated that by 2030, 8/10 will have at least 1 non-HIV related disease (Smit et al., 2015).

# Conclusions

- Older age was associated with a higher prevalence for each individual disease.
- Men vs. Women are more likely to develop Dyslipidemia (PR = 1.25 [1.16-1.34]), Kidney Disease (PR = 3.56 [2.58-4.91]) and Cardiovascular (PR = 2.92 [ 1.03-8.22]).
- IDU vs. MSM less likely to develop Dyslipidemia (PR = 0.81 [0.73-0.90]), Kidney Disease (PR = 0.59 [0.42-0.83]) and Hypertension (PR = 0.59 [ 0.35-0.99])
- Future use of data on mental illness (dementia, depression) and autoimmune diseases.

# THANKS!