

# REVOJUTION

AVANCES Y DESAFÍOS EN EL TRATAMIENTO DEL VIH

# Aging with HIV.

A critical perspective on the future.

Analuz Fernández. Unitat VIH e ITS. Hospital Universitari de Bellvitge. 2025.

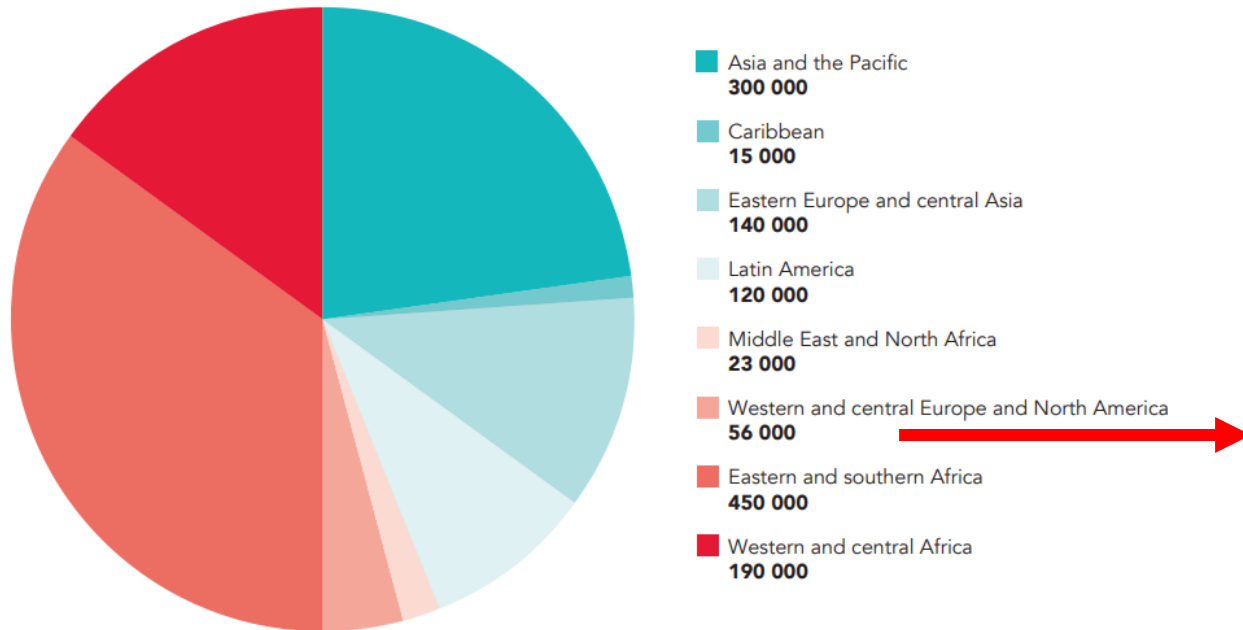


Stepping it up on the streets of New York City, UN Women/Ryan Brown

# People with HIV is increasing.

**1.3 millions [1.0–1.7 millions] new HIV infections around the world.**

**Figure 1.1** Distribution of new HIV infections, by region, 2023



Source: UNAIDS epidemiological estimates, 2024 (<https://aidsinfo.unaids.org/>).

## 2023 DATA

- **24%** decrease in new HIV infections since 2010
- **34%** decrease in AIDS-related deaths since 2010

- People living with HIV:  
**2.3 million**  
[2.0 million–2.7 million]

- New HIV infections:  
**56 000** [45 000–67 000]

- AIDS-related deaths:  
**13 000** [9 400–17 000]

The group of PWHIV over-50 is increasing rapidly.

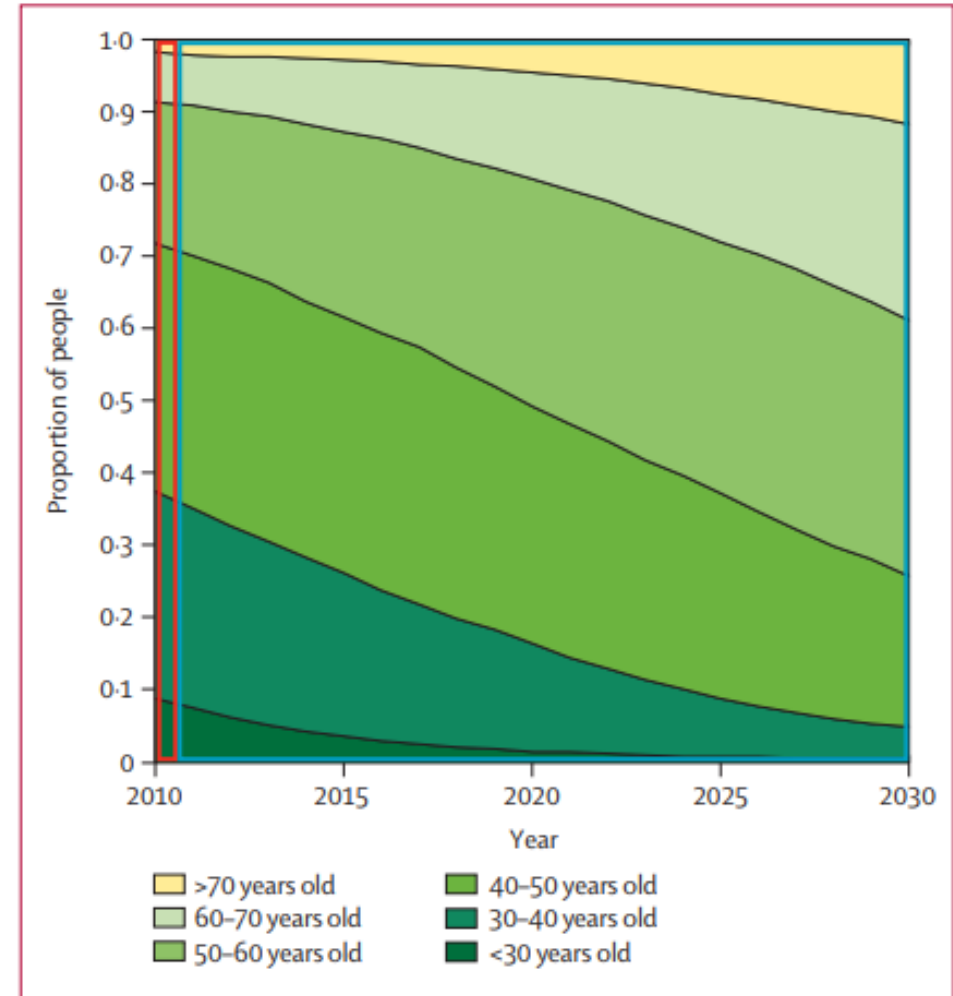


Figure 2: Projected age distribution of HIV-infected patients

Lancet Infect Dis. 2015;15(7):810-818.

Progressively, more PWHIV will be over 50.




**GEPPPO**

FUNCFRAIL cohort study (GeSIDA 9817)



# Dogma N° 1: “Aging in PWHIV is accentuated and accelerated.”









## Excess burden of age-associated comorbidities among people living with HIV in British Columbia, Canada: a population-based cohort study

Ni Gusti Ayu Nanditha <sup>1,2</sup>, Adrianna Paiero,<sup>1</sup> Hiwot M Tafessu,<sup>1</sup> Martin St-Jean,<sup>1</sup> Taylor McLinden,<sup>1</sup> Amy C Justice,<sup>3,4</sup> Jacek Kopec,<sup>5,6</sup> Julio S G Montaner,<sup>1,2</sup> Robert S Hogg,<sup>1,7</sup> Viviane D Lima<sup>1,2</sup>

## Premature Age-Related Comorbidities Among HIV-Infected Persons Compared With the General Population

Giovanni Guaraldi,<sup>1</sup> Gabriella Orlando,<sup>1</sup> Stefano Zona,<sup>1</sup> Marianna Menozzi,<sup>1</sup> Federica Carli,<sup>1</sup> Elisa Garlassi,<sup>1</sup> Alessandra Berti,<sup>2</sup> Elisa Rossi,<sup>2</sup> Alberto Roverato,<sup>3</sup> and Frank Palella<sup>4</sup>

## A matched cohort study investigating premature, accentuated, and accelerated aging in people living with HIV

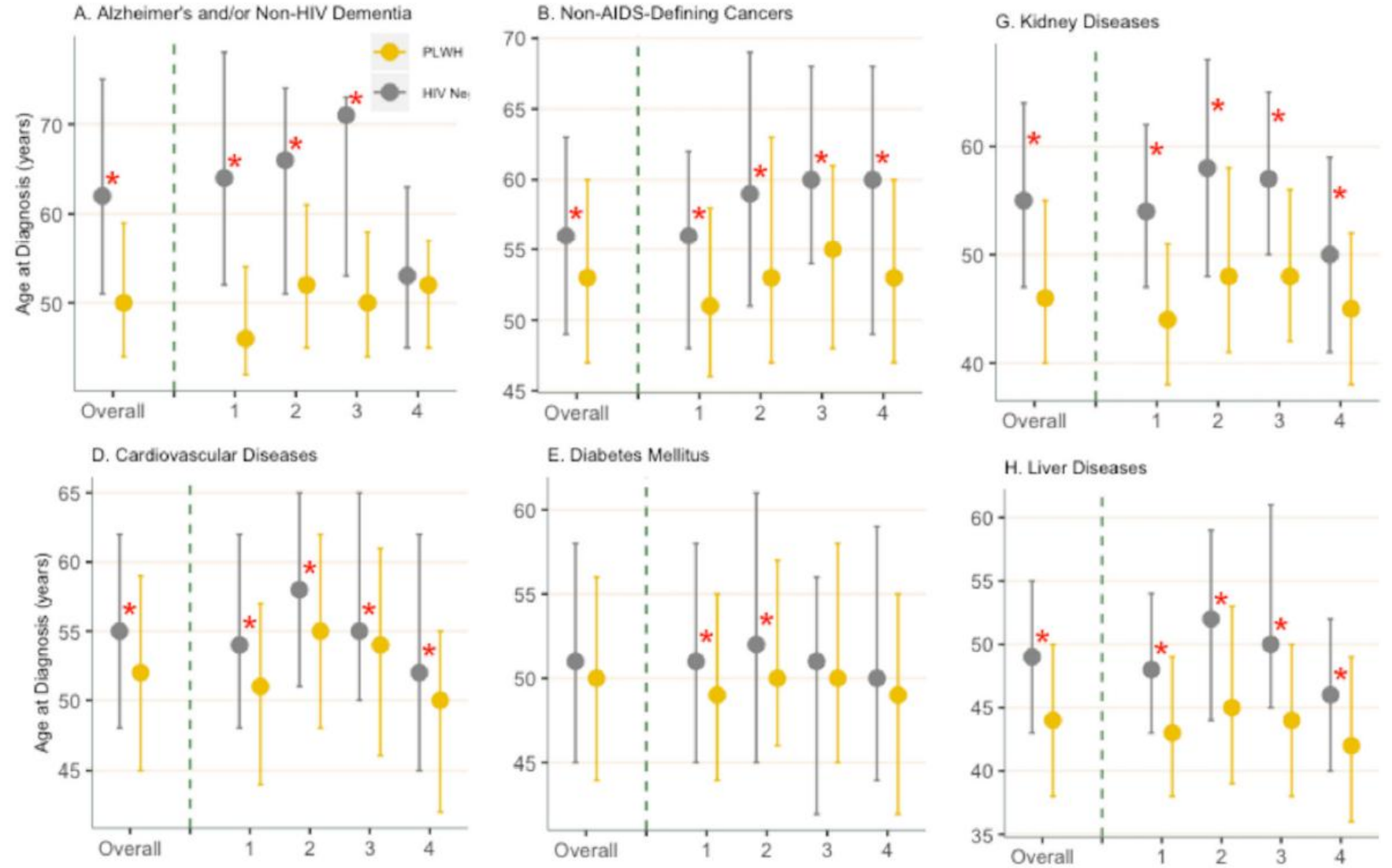
Tiffany E. Gooden<sup>1</sup>  | Jingya Wang<sup>1</sup>  | Dawit T. Zemedikun<sup>1</sup>  | Stephen Taylor<sup>1,2</sup>  | Sheila Greenfield<sup>1</sup>  | Semira Manaseki-Holland<sup>1</sup>  | Krishnarajah Nirantharakumar<sup>1</sup>  | G. Neil Thomas<sup>1</sup> 

Original Investigation | Infectious Diseases

## Aging-Related Comorbidity Burden Among Women and Men With or At-Risk for HIV in the US, 2008-2019

Lauren F. Collins, MD, MSc; Frank J. Palella Jr, MD; C. Christina Mehta, PhD; JaNae Holloway, MSPH; Valentina Stosor, MD; Jordan E. Lake, MD; Todd T. Brown, MD, PhD; Elizabeth F. Topper, PhD; Susanna Naggie, MD; Kathryn Anastos, MD; Tonya N. Taylor, PhD; Seble Kassaye, MD; Audrey L. French, MD; Adaora A. Adimora, MD; Margaret A. Fischl, MD; Mirjam-Colette Kempf, PhD; Susan L. Koletar, MD; Phyllis C. Tien, MD; Ighovwerha Ofotokun, MD; Anandi N. Sheth, MD, MSc

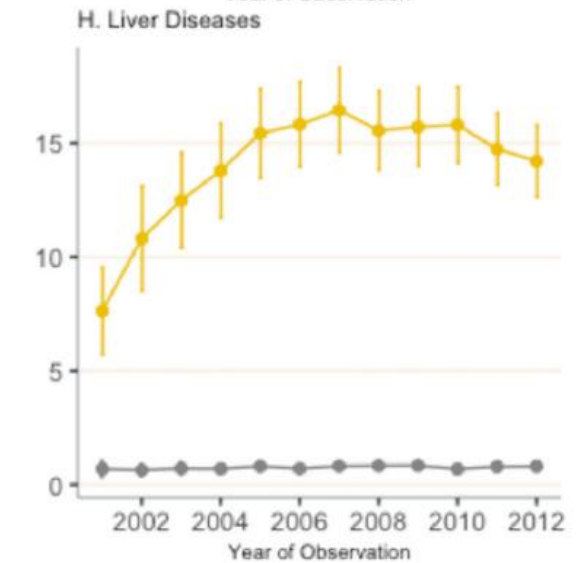
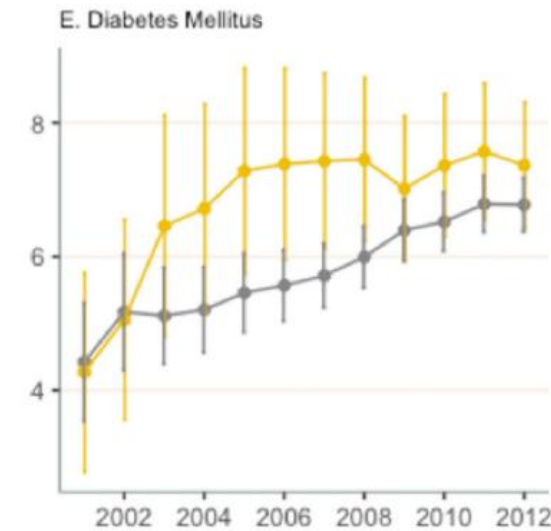
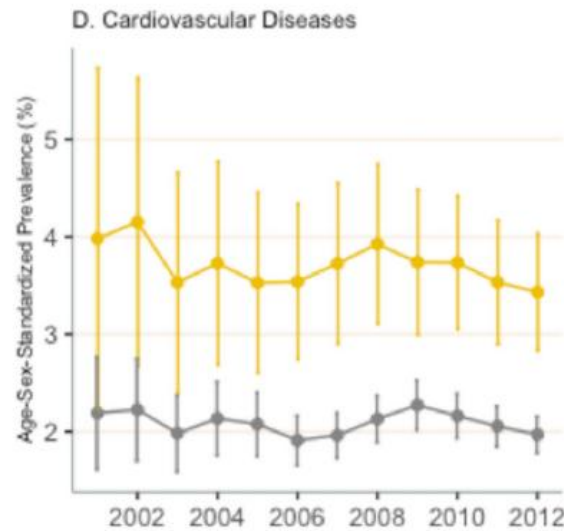
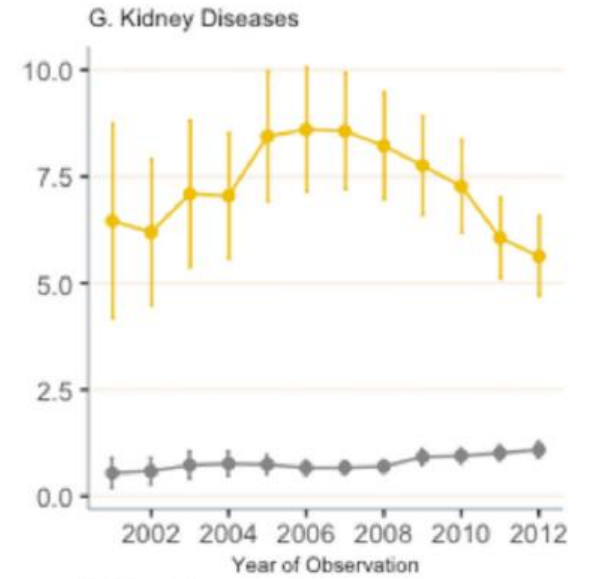
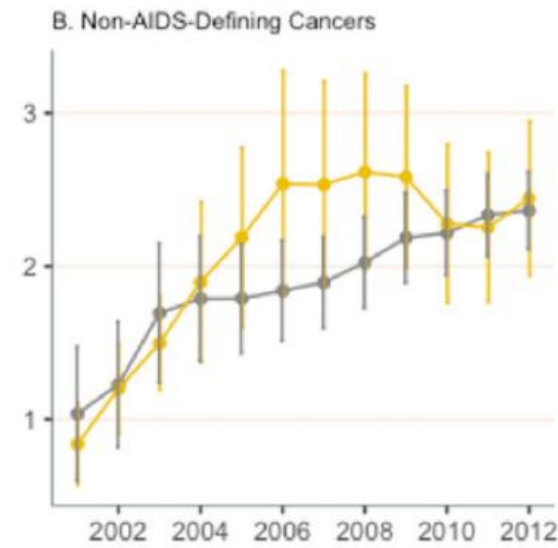
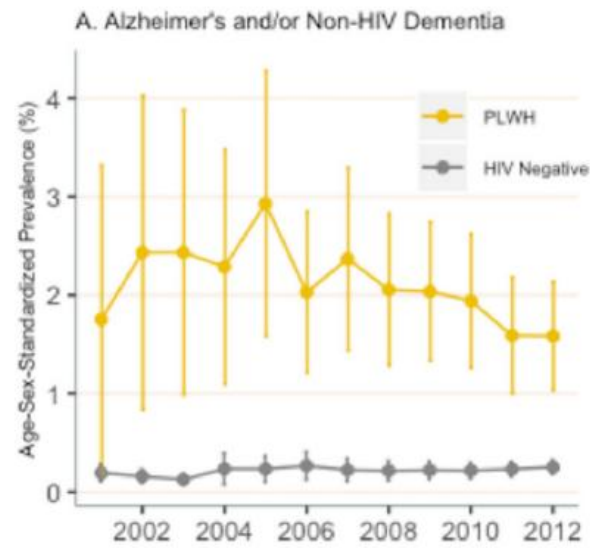
# Aging in PWHIV is accelerated.



Nanditha NGA, et al. BMJ Open 2021.

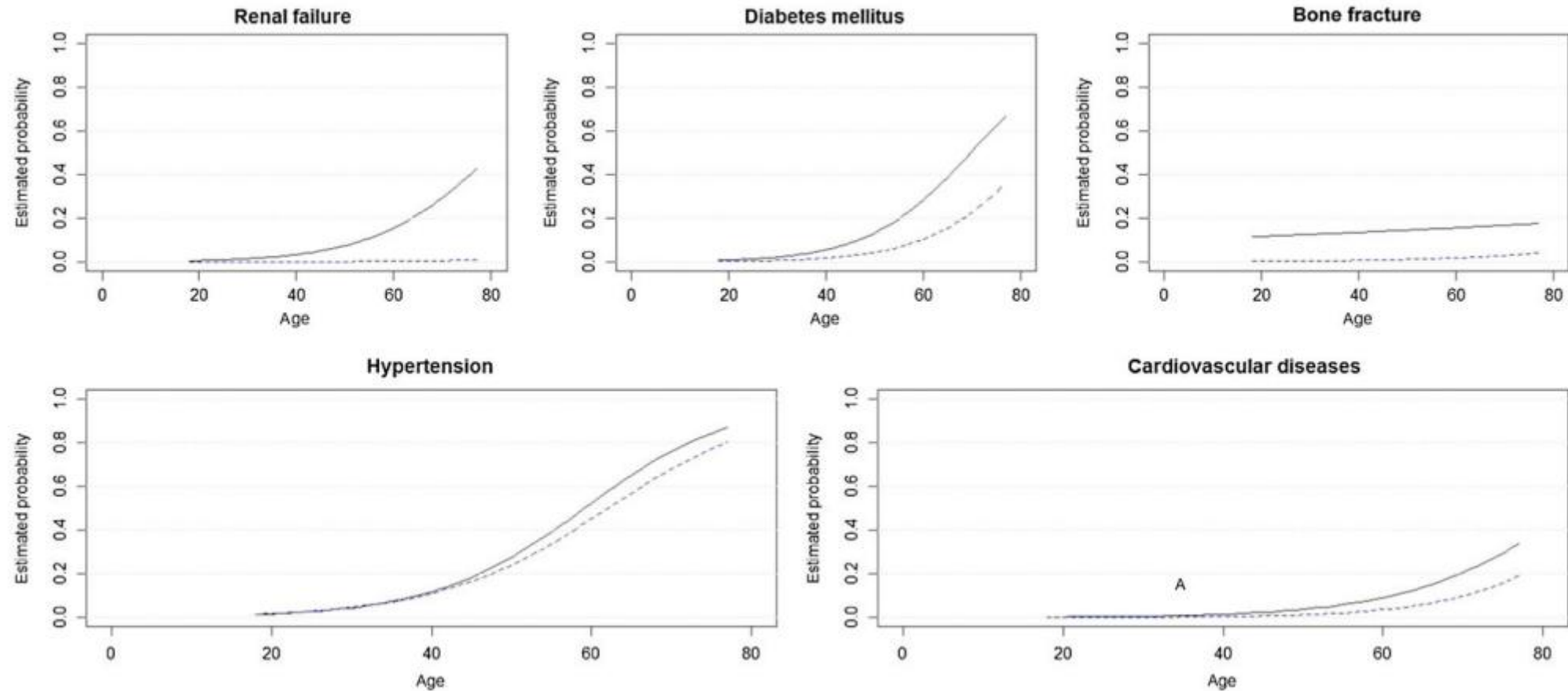


# Aging in PWHIV is accentuated.



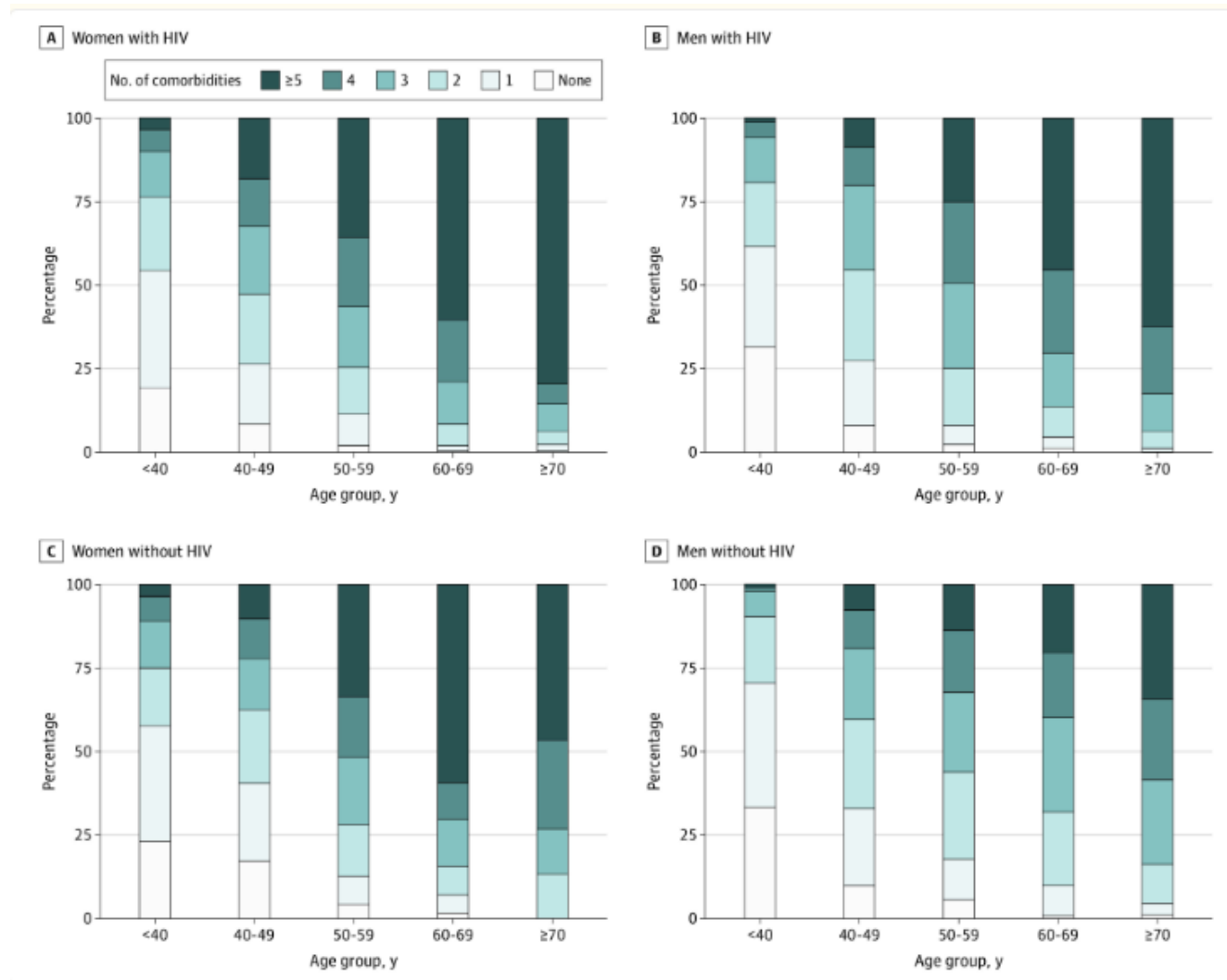
Nanditha NGA, et al. BMJ Open 2021.

Comparative risk of hypertension, diabetes mellitus, CKD, CVD, and fracture, by age, among patients versus control subjects.



Guaraldi. CID, 2011.

# Distribution of Prevalent Non-AIDS Comorbidity Burden by HIV Serostatus, Sex, and Age Group



Collins LF., JAMA, 2023.

LEARN THE **DOGMA** LIKE A  
PRO.  
SO YOU CAN BREAK  
THEM LIKE AN **SCIENTIST**

Pablo Picasso



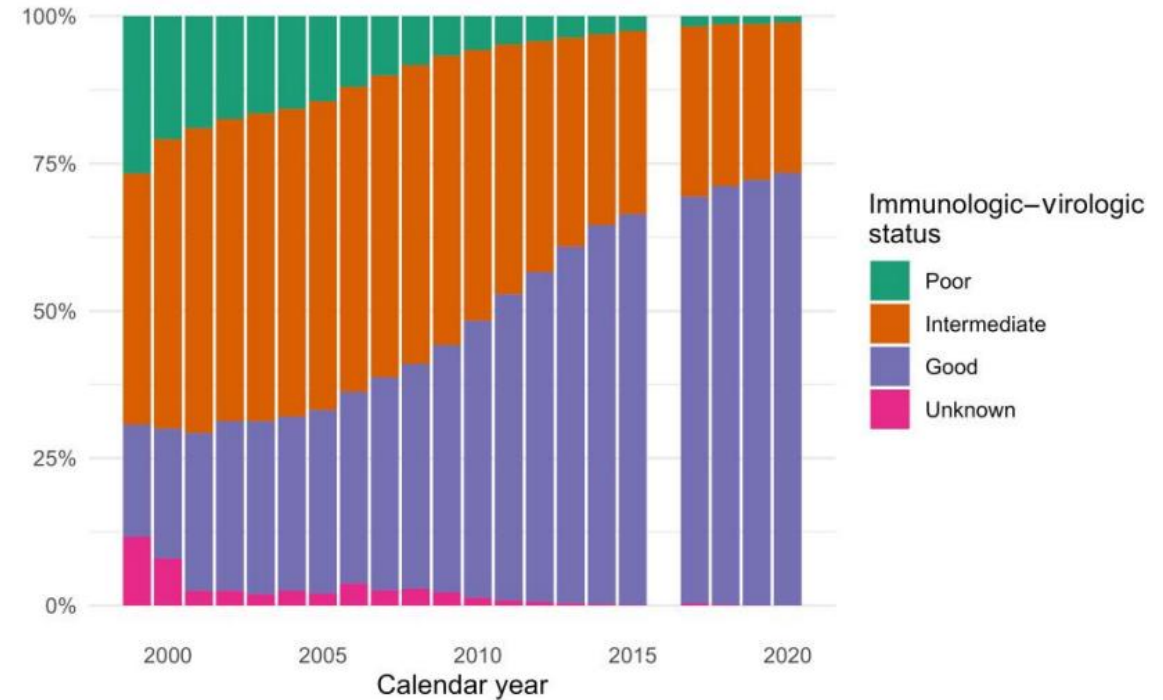
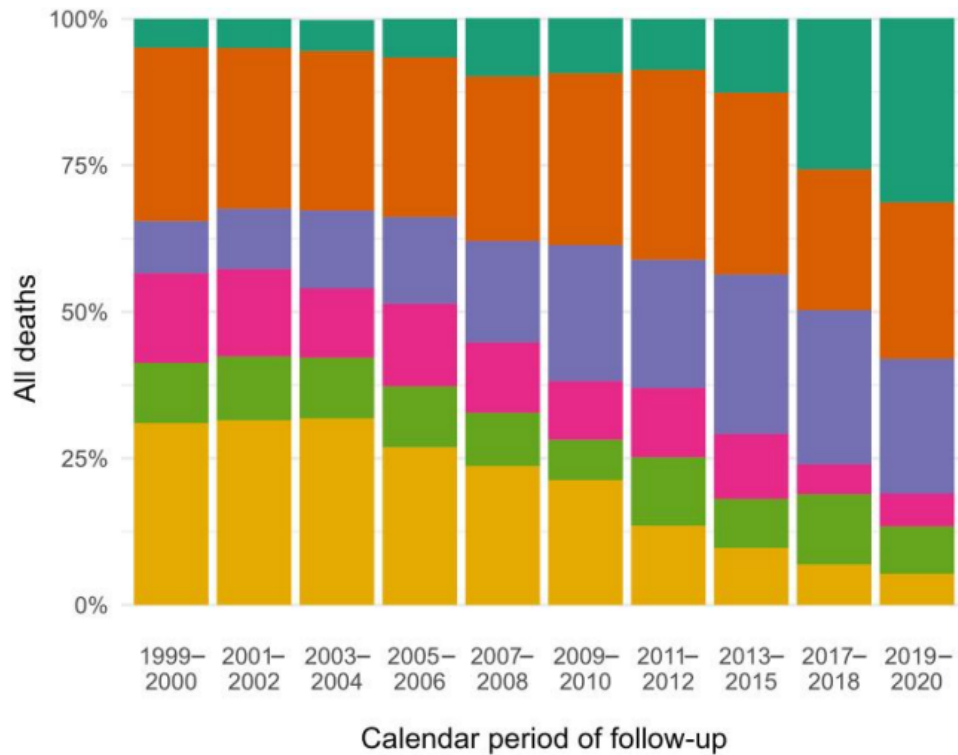
# Is aging in PWHIV the same in all cases?

Country	Italy	Canada	UK	USA
N (PWHIV)	2854	8031	8880	5929
Observation period.	2002-2009	2000-2012	2000-2020	2008-2019
Reference	Guaraldi. CID, 2011.	Nanditha NGA. BMJ Open 2021.	Gooden TE. HIV Med. 2023.	Collins. JAMA, 2023.

Until 2015 (START study), initiation of ART was delayed until advanced stages.

Use of older NRTIs until 2013-2014 (and beyond)- No use of INSTI until 2016-2017

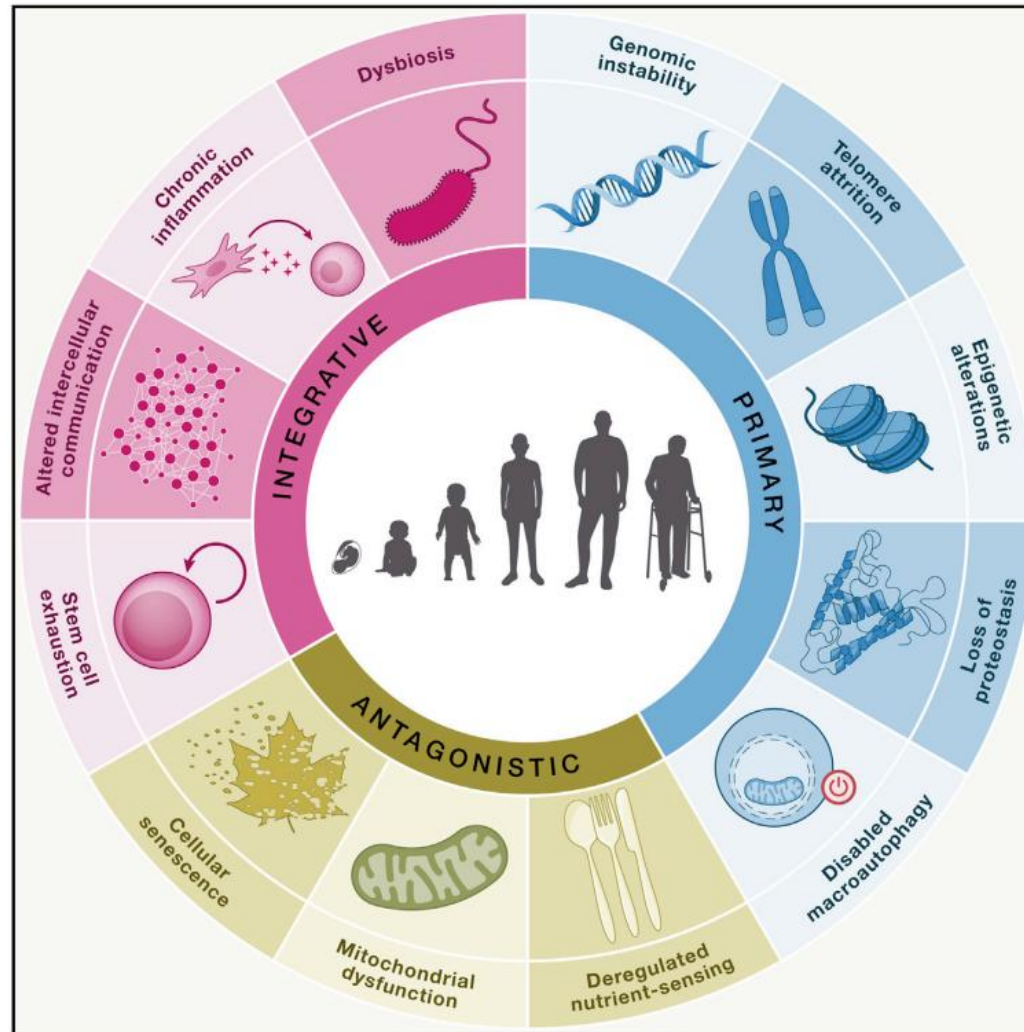
# Dogma N° 2: “Ageing in PWHIV is different from the HIV-negative population, **regardless of ART**”.



Are all the antiretroviral drugs the same?

Tusch. CID, 2025.

# Are all the antiretroviral drugs the same?



López-Otín, Cell, 2023.

# Genomic Instability.



## Genome is exposed to sources of damage.

### Extrinsic sources.

- chemical, physical, and biological agents.

### Intrinsic sources.

- Replication errors, chromosome segregation defects, oxidative processes

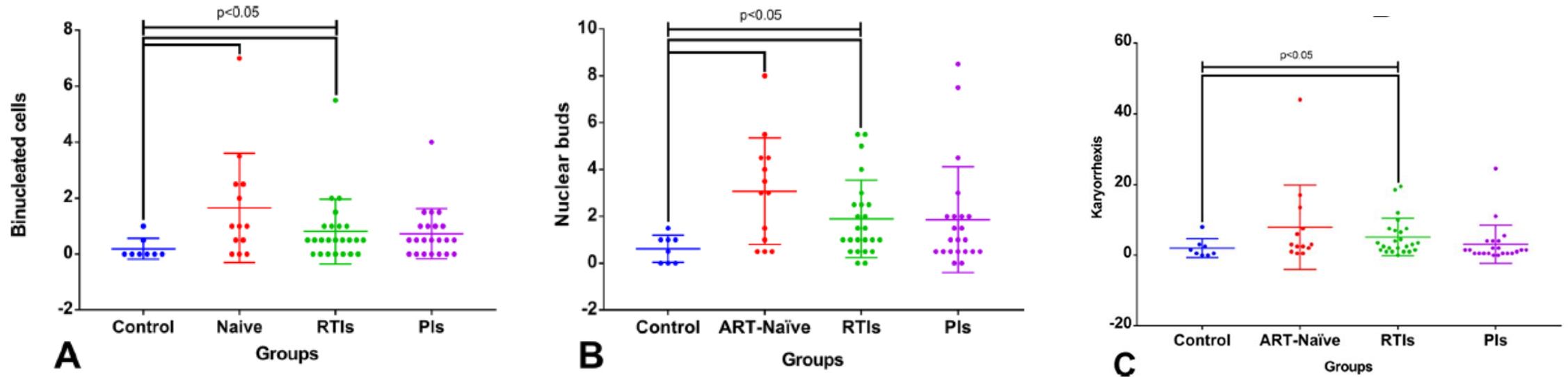
Apoptosis  
Senescence  
Malignancy

Reduced tissue repair capacity; altered functions → **Aging**

Moskalev, Ageing Res Rev, 2013.; Gutiérrez-Sevilla, Mutat Res Genet Toxicol Environ Mutagen, 2021.; Lima, J Oral Pathol Med, 2017.



PWHIV appear to exhibit greater genomic instability.  
Different treatments show different outcomes.



NNRTIs: **EFV** + ABC/3TC or TDF/FTC  
PIs: **LPV/r** or **ATV/r** + TDF/FTC

Gutiérrez-Sevilla, Mutat Res Genet Toxicol Environ Mutagen, 2021

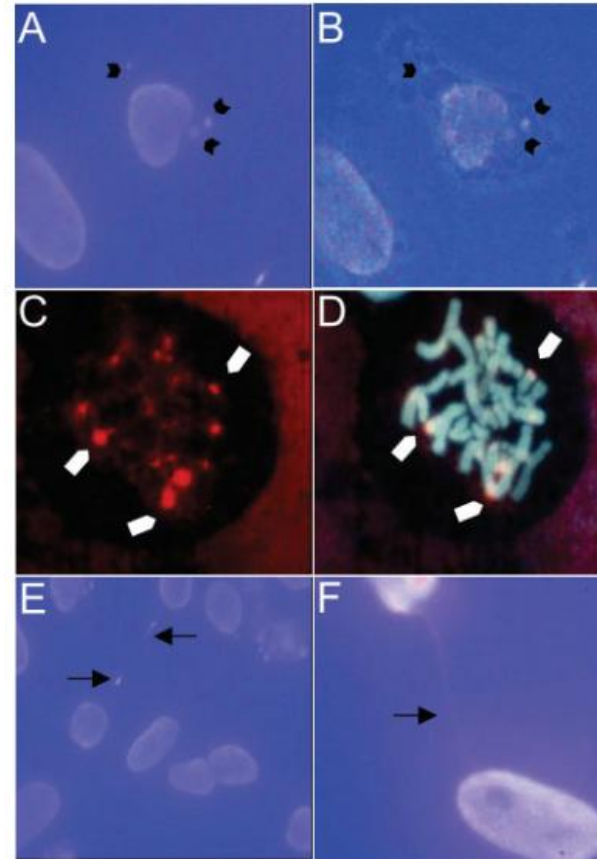
# Genomic instability in mtDNA: the role of older NRTIs.

AZT, D4T are incorporated into nDNA and mDNA.

Micronuclei, chromatid exchange and chromosomal aberrations.

Deletions and point-mutations.  
Oxidative damage.

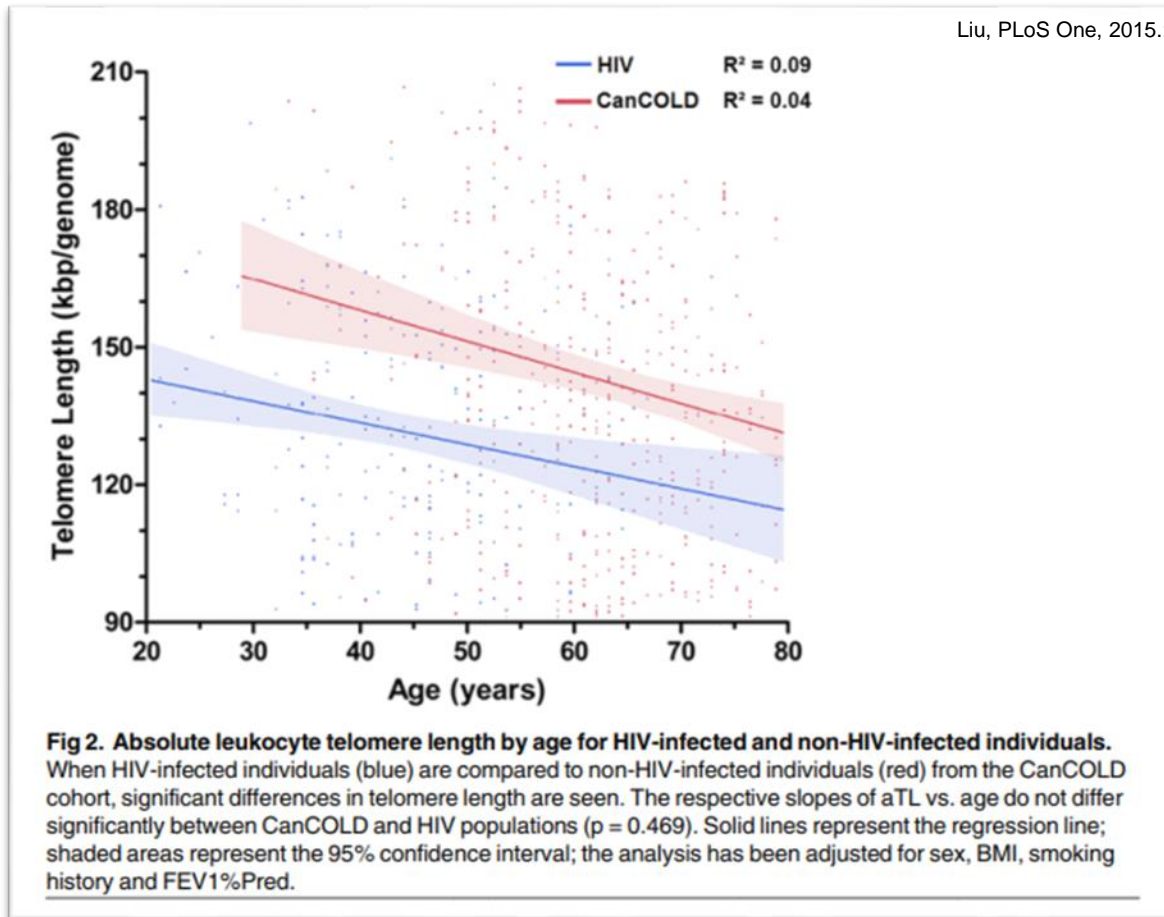
**Ageing.**



**Current  
ART?**

Olivero. Environmental and Molecular Mutagenesis, 2007; Liang. International Journal of Antimicrobial Agents. 2017,

# Telomere attrition in PWHIV.



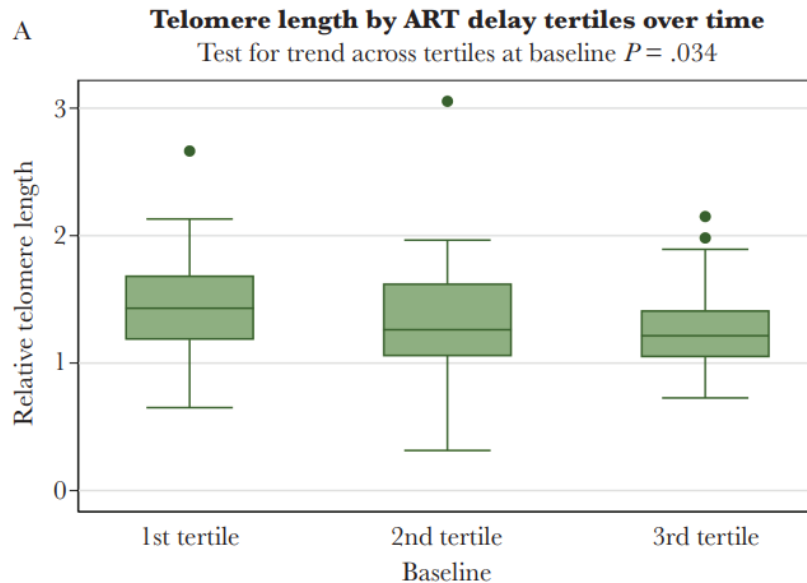
- Begins in early stages of infection (1, 3, 4)
- Greater shortening when baseline CV >1000000 copies and CD4 < 200 Cél/s X10E6/L (1, 2)
- The **timing** of ART initiation and **choice** matter. (2, 3)

Liu, PLoS One, 2015.; Gonzalez-Serna, J Acquir Immune Defic Syndr, 2017; Leung, Aging (Albany NY), 2017; Stella-Ascariz, JID, 2018.

# Telomere attrition: The role of **timing** of ART initiation.

## Impact of Delaying Antiretroviral Treatment During Primary Human Immunodeficiency Virus Infection on Telomere Length

Marieke Raffenberg,<sup>1,2,a</sup> Tanja Engel,<sup>1,3,a</sup> Isabella C. Schoepf,<sup>1,4</sup> Neeltje A. Kootstra,<sup>4</sup> Peter Reiss,<sup>5</sup> Dominique L. Braun,<sup>7</sup> Christian W. Thorball,<sup>6,8</sup> Jacques Fellay,<sup>6,8</sup> Roger D. Kouyos,<sup>7,9</sup> Bruno Ledergerber,<sup>7</sup> Huldrych F. Günthard,<sup>7,9,\*</sup> and Philip E. Tarr<sup>1,9</sup>; for the Zurich Primary HIV Infection Study and the Swiss HIV Cohort Study



Acute HIV infection  
Delaying TAR: 25, 42 y 65 days.

In **6-year** follow-up, this difference was more pronounced ( $P = 0.001$ ) and remained significant as long as there were **no interruptions** longer than 12 months.




Telomere attrition is associated with high risk of comorbidities in PWHIV.

Raffenberg, J Infect Dis, 2021.; Liu, PLoS One, 2015; Engel, Clin Infect Dis, 2021.; Mehta, Drug Alcohol Depend, 2021

# Telomere attrition: **ART choice** matters.

- **NRTIs (both Tenofovir and abacavir)** are associated with telomerase inhibition *in vitro* (1).
- Use of **Tenofovir** for more than 4 years is associated with Shorter telomeres and less telomerase activity compared to Tenofovir-sparing regimens (2).

## Blood telomere length gain in people living with HIV switching to dolutegravir plus lamivudine versus continuing triple regimen: a longitudinal, prospective, matched, controlled study

Francesca Lombardi <sup>1\*</sup>, Alessia Sanfilippo<sup>2</sup>, Massimiliano Fabbiani <sup>3</sup>, Alberto Borghetti<sup>1</sup>, Arturo Ciccullo <sup>4</sup>, Enrica Tamburrini<sup>1,2</sup> and Simona Di Giambenedetto<sup>1,2</sup>

	Entire population <i>n</i> =120	DT <i>n</i> =60	TT <i>n</i> =60	<i>P</i>
Backbone, <i>n</i> (%)				0.709
FTC/TDF or FTC/TAF <sup>d</sup>	72 (60.0)	35 (58.3)	37 (61.7)	
ABC/3TC	48 (40.0)	25 (41.7)	23 (38.3)	

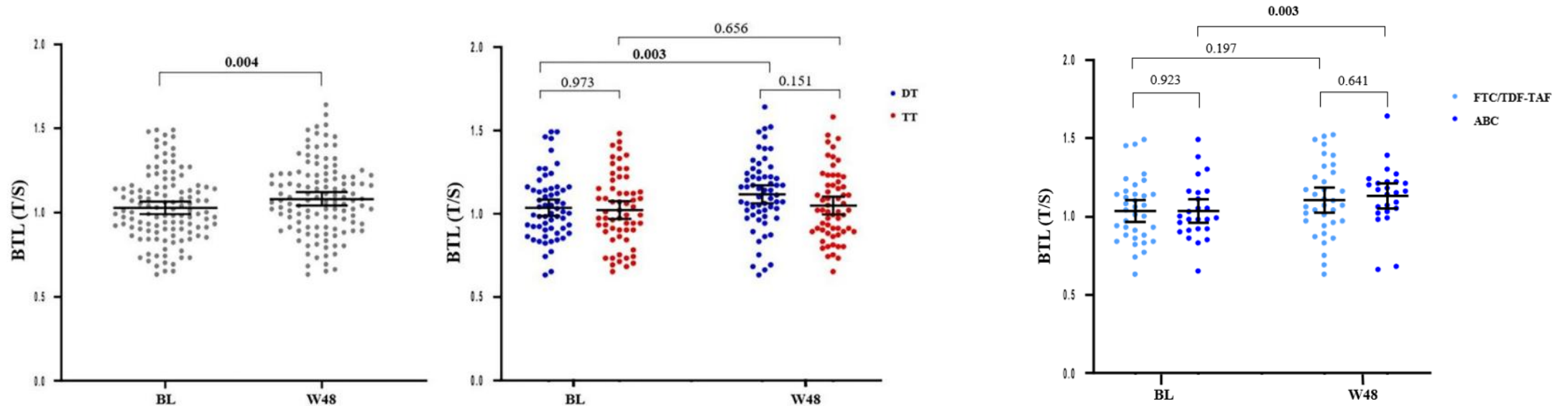
1. Leeansyah E. J Infect. Dis. 2013.

2. Rodríguez-Centeno; J Antimicrob Chemother 2022

# Telomere attrition: ART choice matters.

**Blood telomere length gain in people living with HIV switching to dolutegravir plus lamivudine versus continuing triple regimen: a longitudinal, prospective, matched, controlled study**

Francesca Lombardi <sup>1\*</sup>, Alessia Sanfilippo<sup>2</sup>, Massimiliano Fabbiani <sup>3</sup>, Alberto Borghetti<sup>1</sup>, Arturo Ciccullo <sup>4</sup>, Enrica Tamburrini<sup>1,2</sup> and Simona Di Giambenedetto<sup>1,2</sup>





# Epigenetic changes.

- ✓ Alterations in DNA methylation patterns, histone modification, and chromatin remodeling <sup>(1)</sup>.
- ✓ Calculation of biological age through clocks <sup>(1-4)</sup>



Correlation of the difference between biological and chronological age with time to death, time to coronary disease, cancer, menopause, type 2 diabetes, and visceral fat(3, 4)

1) Fraga, Trends Genet, 2007; 2) Horvath, Genome Biol, 2014; 3) Levine, Aging (Albany NY), 2018.; 4) Lu, Aging (Albany NY), 2019.

# Epigenetic changes in PWHIV

-PVVH naive vs controls without VIH.	-PVVH have higher biological age than controls (between 4 and 15 years).	1, 2
-PVVH before and after ART.	-ART partially reverses the acceleration of biological age. (RAL+DRV/r; TDF/FTC/Drv/r)	3
-PVVH con CV indetectable	-ART prevents the acceleration of biological age. A higher biological age could predict clinical events. (RAL+DRV/r; TDF/FTC/Drv/r)	4

Current ART?

1) Yang, J Infect Dis, 2021.; 2) Rickabaugh, PLoS One, 2015; 3) Esteban-Cantos, J Infect Dis, 2021; 4) Esteban-Cantos, Lancet HIV, 2021; 5)Shiau, Clin Infect Dis, 2021.



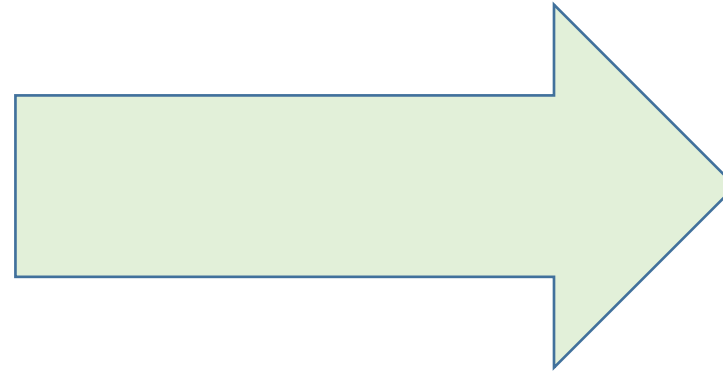
# Inflammaging.

Modified gut microbiota.

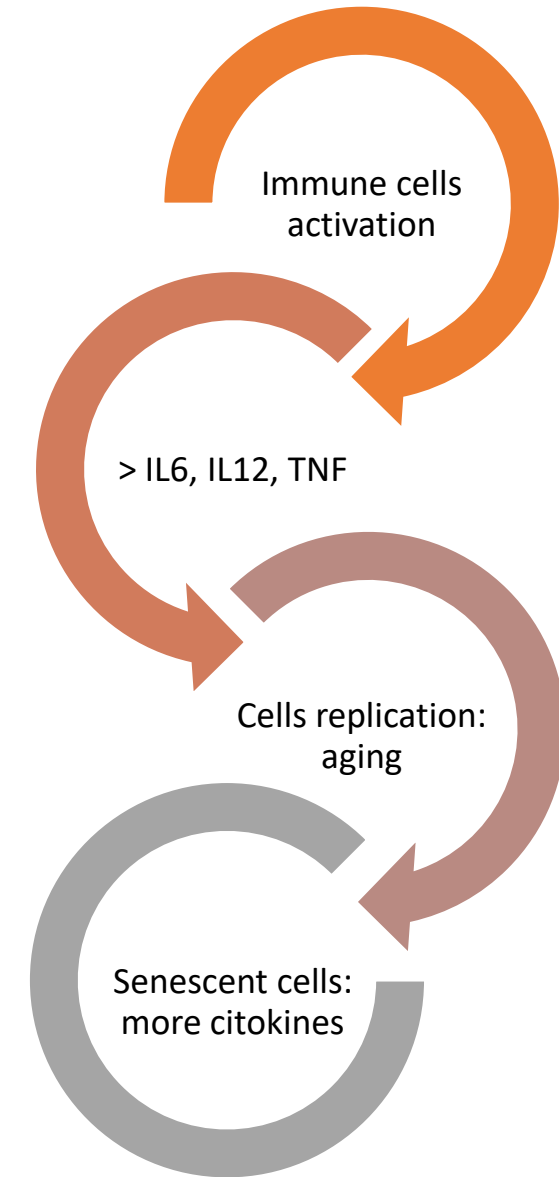
Circulating non-infective virions.

Reservoirs.

Coinfections (CMV; VHC; VHB; etc)



Comorbidities –  
Immuno-senescence.

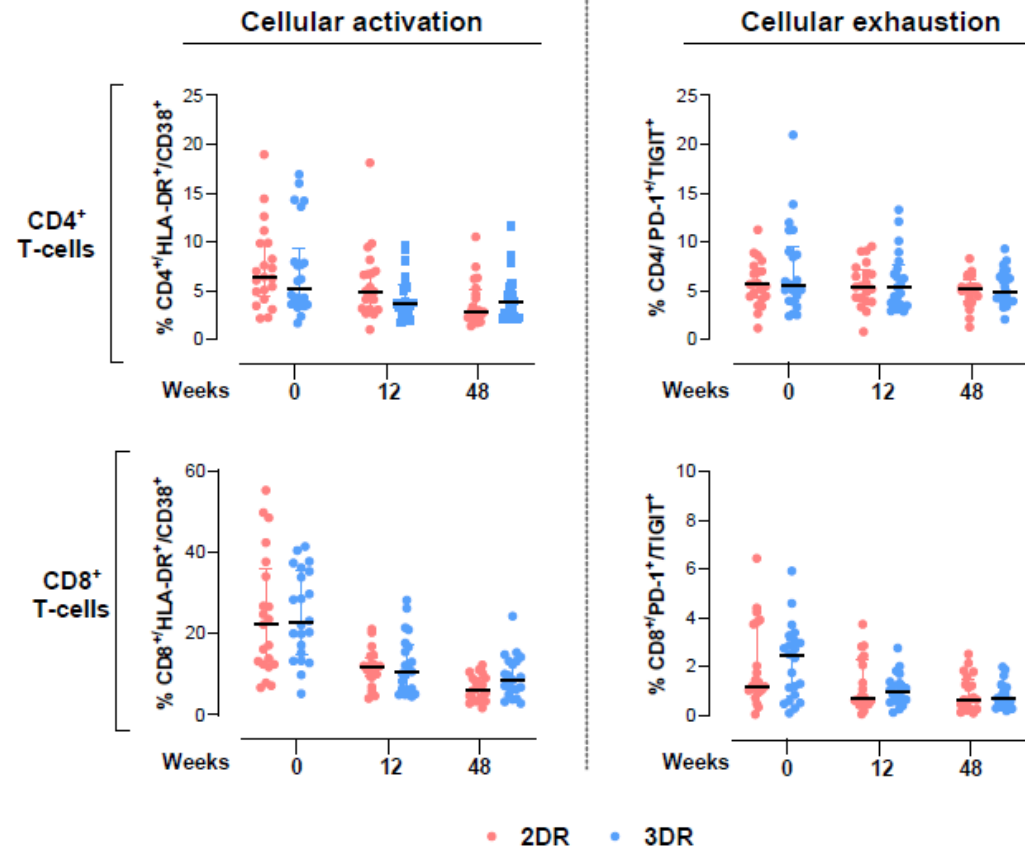


Sauce, Medicine (Baltimore), 2021; Kuller, PLoS Med, 2008; Prabhu, Front Immunol, 2019; Moir, Curr Opin HIV AIDS, 2014

# Inflammaging differences between ART

## Evolution of immune activation and exhaustion markers.

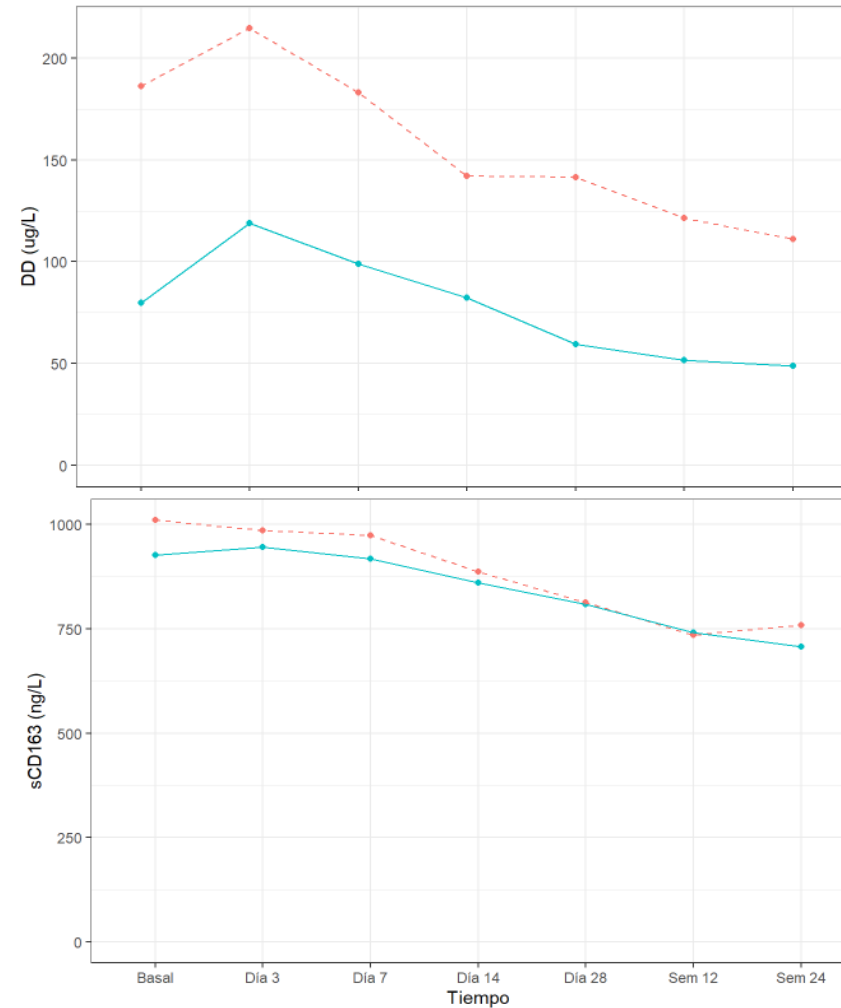
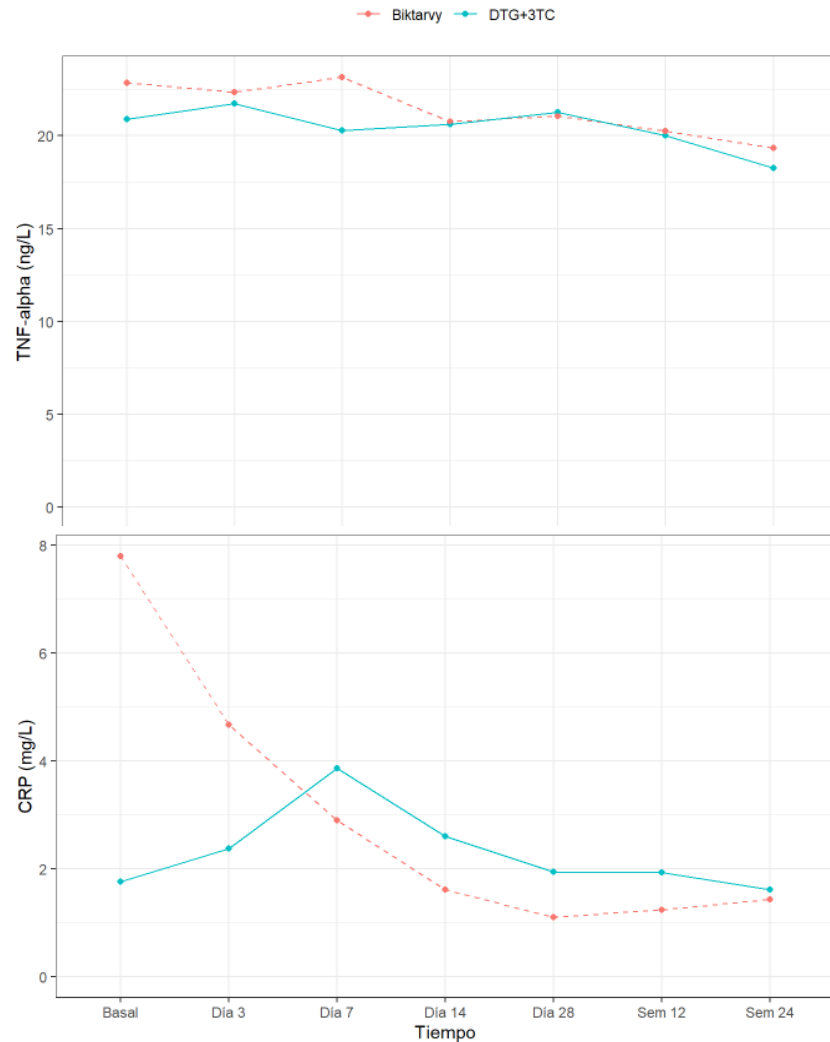
Median and IQR are shown.



\*: DTG/3TC vs DTG+F/TAF

Moltó J. P647. CROI, 2024.

# Inflammaging differences between ART: DTG/3TC vs BIC/F/TAF

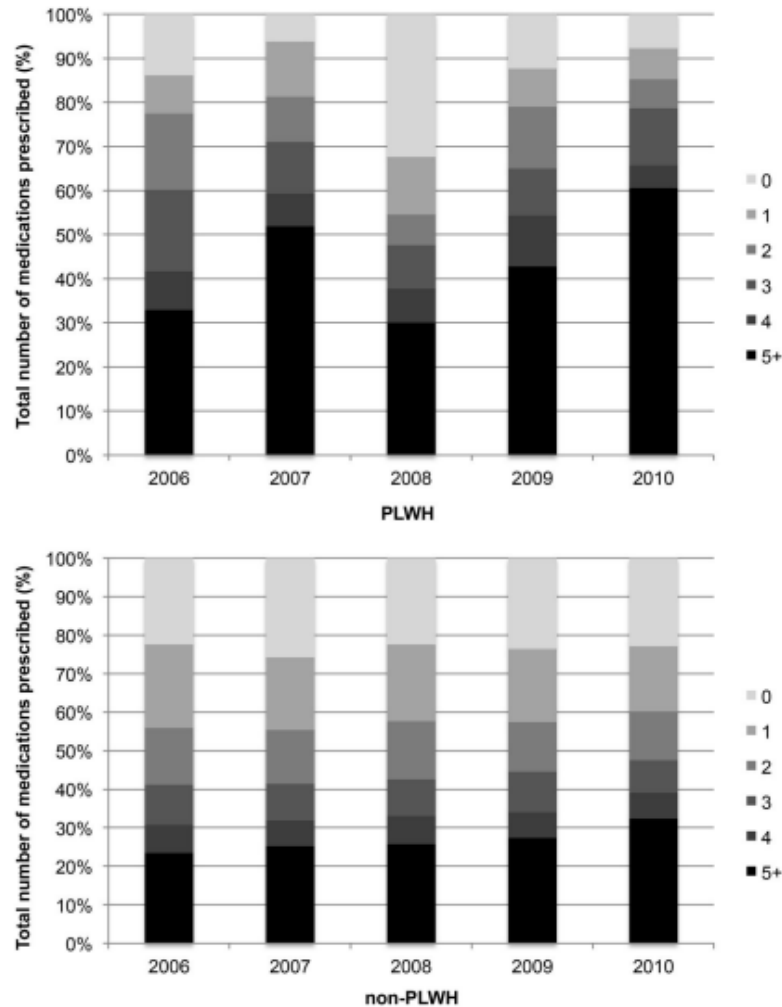


Fernández A. P641. Glasgow, 2024.

Dogma N° 2: “Ageing in PWHIV is different from the HIV-negative population, **regardless of ART**”.

Work in progress...

# Dogma Nº 3: Polipharmacy is more common in PWHIV.



-Lower adherence.  
-More adverse events, hospitalizations, geriatric syndroms, mortality.  
-Potential drug-drug interactions.

Figure 1. Annual number of outpatient medications prescribed to PLWH and non-PLWH.



Morillo-Verdugo R. *Enferm Infecc Microbiol Clin (Engl Ed)*. 2022; Edelman EJ. *Drugs Aging*. 2013; Bastida C. *Farm Hosp*. 2017; Contreras-Macías E. *Enferm Infecc Microbiol Clin (Engl Ed)*. 2023

# To **de**prescribe or to **over**prescribe?

## Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H., Gerald S. Bloomfield, M.D., M.P.H., Judith S. Currier, M.D., Esteban Martinez, M.D., Ph.D., Jhoanna C. Roa, M.D., Marissa R. Diggs, B.A., Evelynne S. Fulda, B.A., Kayla Paradis, M.B.A., Stephen D. Wiviott, M.D., Borek Foldyna, M.D., Sara E. Looby, Ph.D., Patrice Desvigne-Nickens, M.D., Beverly Alston-Smith, M.D., Jorge Leon-Cruz, M.S., Sara McCallum, M.P.H., Udo Hoffmann, M.D., M.P.H., Michael T. Lu, M.D., M.P.H., Heather J. Ribaldo, Ph.D., and Pamela S. Douglas, M.D., for the REPRIEVE Investigators\*

## Emerging roles of senolytics/senomorphics in HIV-related co-morbidities

Gagandeep Kaur<sup>a</sup>, Md. Sohanur Rahman<sup>b</sup>, Sadiya Shaikh<sup>a</sup>, Kingshuk Panda<sup>b</sup>, Srinivasan Chinnapaiyan<sup>b</sup>, Maria Santiago Estevez<sup>b</sup>, Li Xia<sup>a</sup>, Hoshang Unwalla<sup>b</sup>, Irfan Rahman<sup>a</sup>  

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## Once-weekly semaglutide in people with HIV-associated lipohypertrophy: a randomised, double-blind, placebo-controlled phase 2b single-centre clinical trial

Allison Ross Eckard, Qian Wu, Abdus Sattar, Kianoush Ansari-Gilani, Danielle Labbato, Theresa Foster, Aaron A Fletcher, Ruth O Adekunle, Grace A McComsey



## Genomic Instability Decreases in HIV Patient by Complementary Therapy with *Rosmarinus officinalis* Extracts

Blanca Patricia Lazalde-Ramos<sup>1</sup>, Ana Lourdes Zamora-Perez<sup>2</sup>, Aymée Ileana Ortega-Guerrero<sup>3</sup>, Saira Zulema Quintero-Fraire<sup>3</sup>, Omar Palacios-Lara<sup>4,5</sup>, Sol María Quirarte-Báez<sup>5</sup>, Carlos Galaviz-Hernández<sup>6</sup>, Martha Sosa-Macías<sup>6</sup>, Yveth Marlene Ortiz-García<sup>2</sup>, and Gabriela Morales-Velazquez<sup>2</sup>

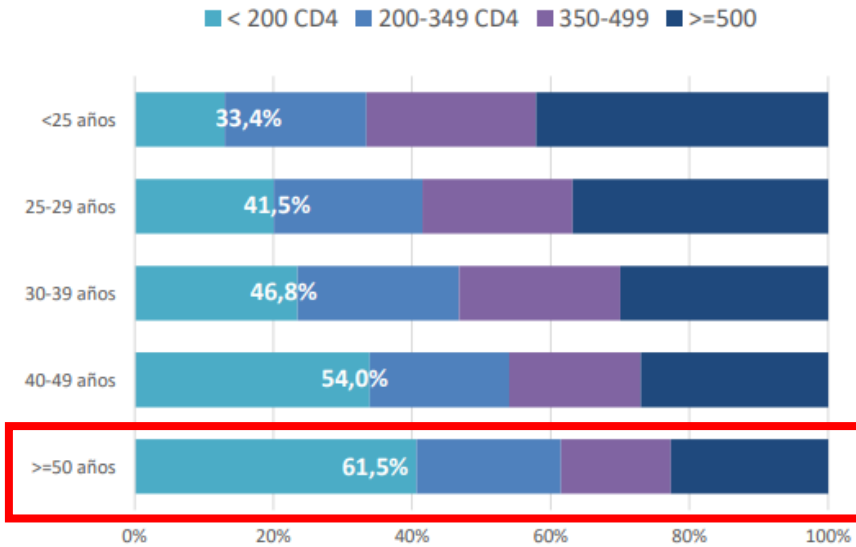
What is the most critical concern?

# VIGILANCIA EPIDEMIOLÓGICA DEL VIH y SIDA EN ESPAÑA 2023

ACTUALIZACIÓN 30 de junio de 2024

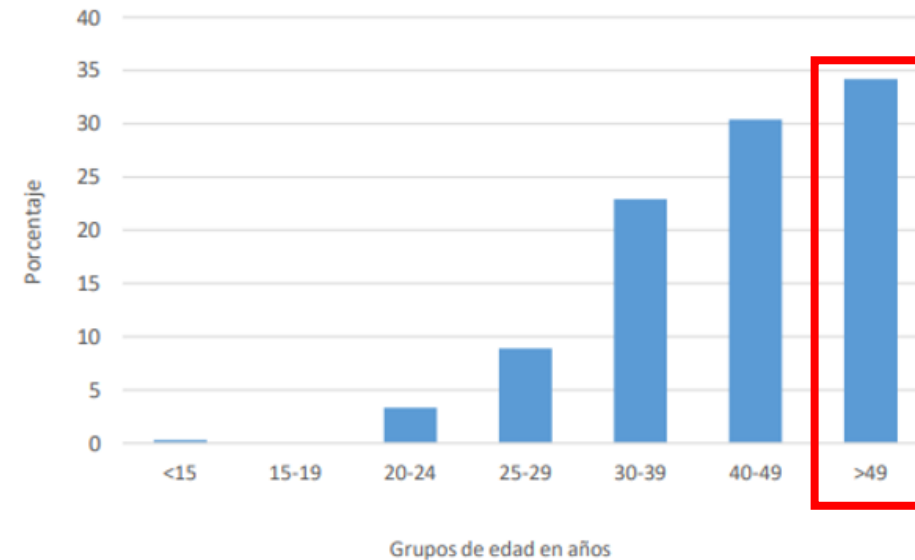
Nuevos diagnósticos de VIH. Diagnóstico tardío según grupo de edad. España, año 2023. Datos no corregidos por retraso en la notificación.

Casos de sida diagnosticados en España\* en 2023. Distribución por edad y sexo. Registro Nacional de Sida. Datos no corregidos por retraso en la notificación.



n= 2.837

Edad



Vigilancia epidemiológica de VIH y SIDA en España 2023 (Actualización junio 2024)

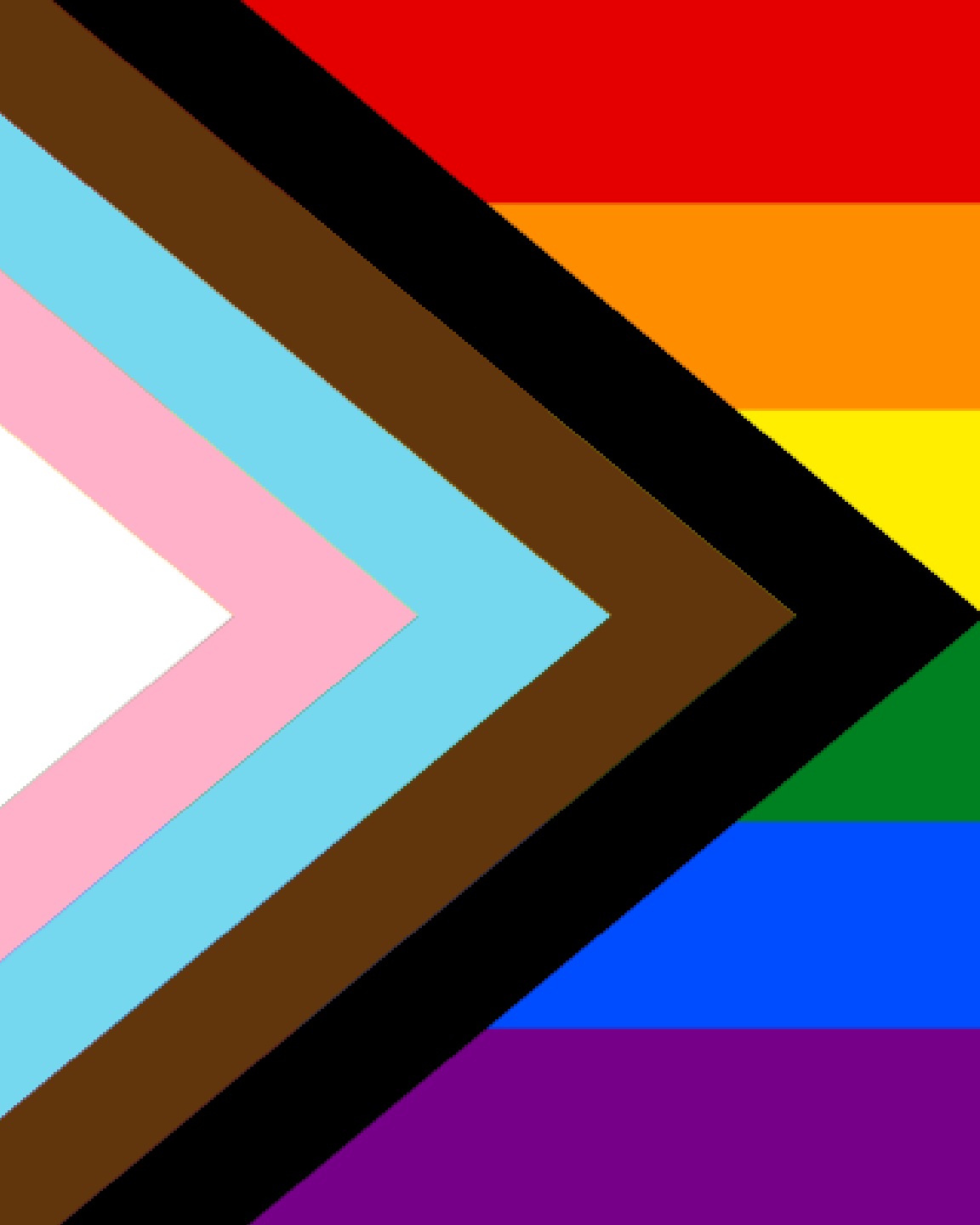




CrossMark

# Ageism: the -ism affecting the lives of older people living with HIV

*Giovanni Guaraldi, Jovana Milic, Mario Cascio, Cristina Mussini, Esteban Martinez, Jules Levin, Daniele Calzavara, Rebecca Mbewe, Julian Falutz, Chloe Orkin, Matteo Cesari, Jeffrey V Lazarus*



Sean eternos los  
**derechos** que  
supimos conseguir.

Muchas gracias.