

AIDS presenters and advanced not-naïve

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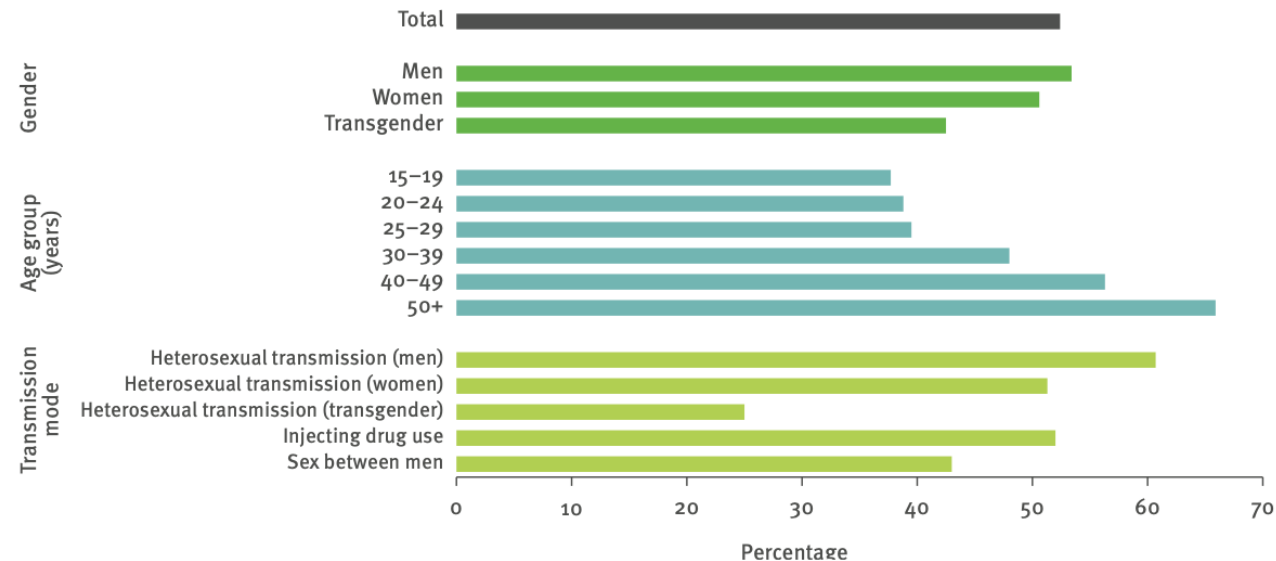
Background

- Despite significant **progress** in the management of **HIV infection** over recent decades, **advanced HIV disease (AHD)** remains a **relevant public health issue**, contributing substantially to **morbidity** and **mortality** among people with HIV (PWH)
- **AHD** is defined as:
 - CD4 T-cell count < **200 cells/mm³**
and/or
 - the presence of an **AIDS-defining event (ADE)**

Background

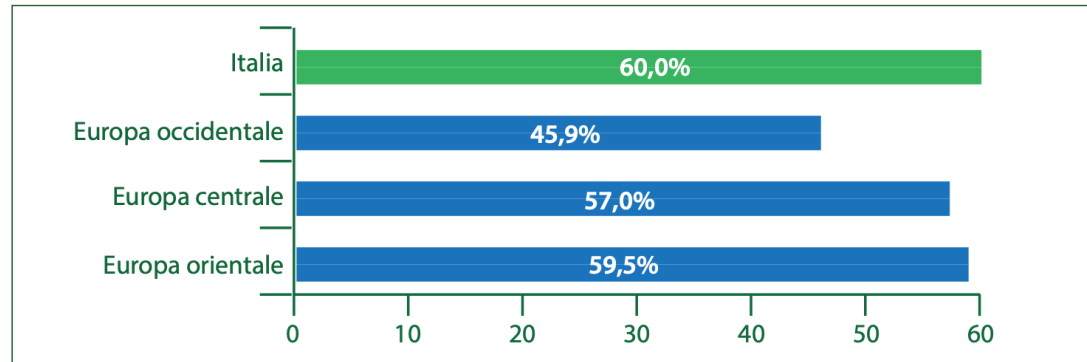
In the **European Region**, more than half of HIV diagnoses have a **CD4 cell count < 350 cells/mm³**, including almost a **third of cases with advanced HIV infection (CD4 cell count < 200/mm³)** at the time of diagnosis

Fig. B. Proportion of people diagnosed late (CD4 cell count < 350 per mm³) by gender, age and transmission mode, WHO European Region, 2023



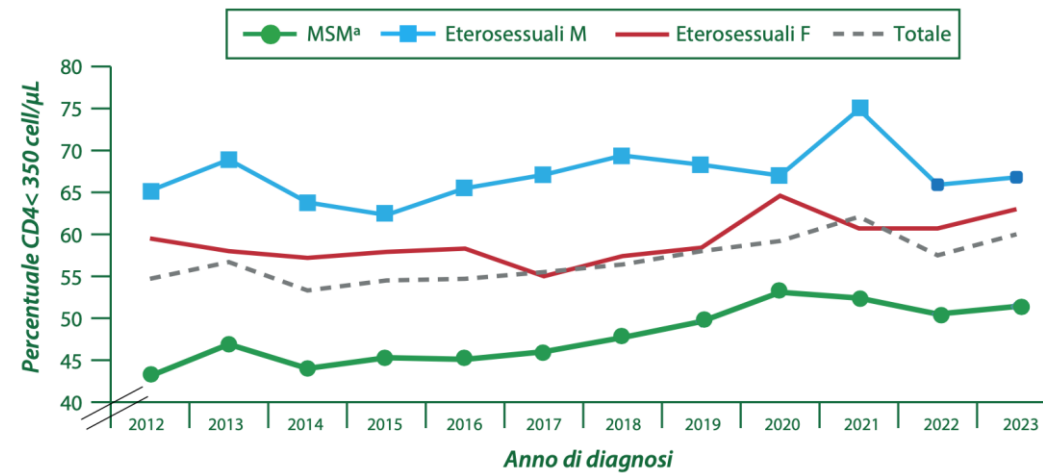
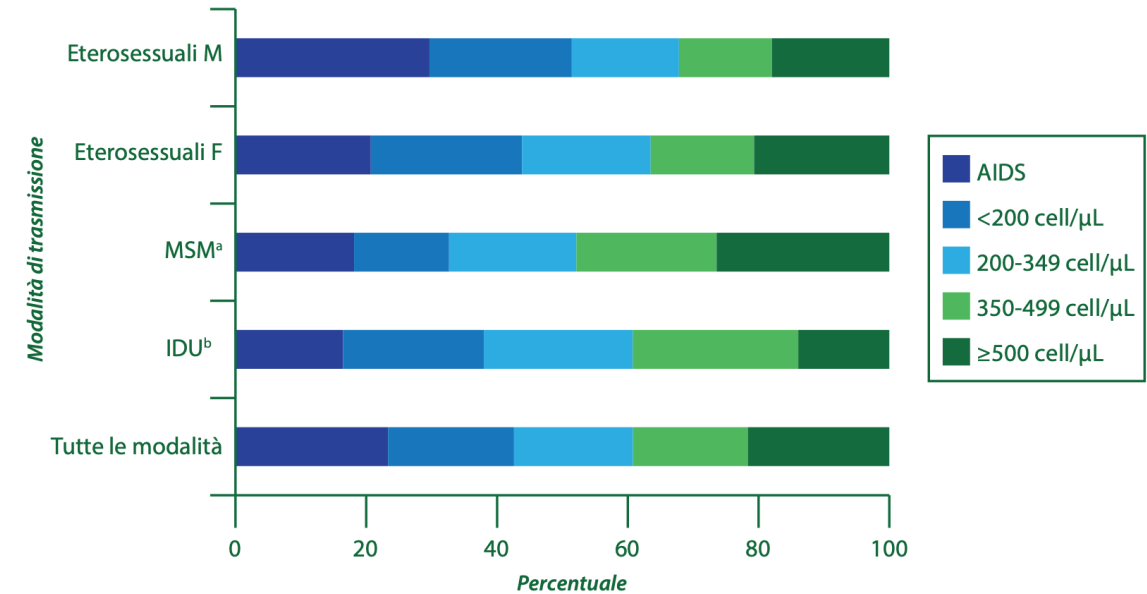
Background

Late presenters 2023*



(*) *Late presenters*: nuove diagnosi di infezione da HIV con numero di linfociti CD4 <350 cell/μL.

Fonti: Sistema di Sorveglianza HIV nazionale, ECDC/WHO. HIV/AIDS Surveillance in Europe 2024-2023 data (1)



Background

- **AHD** is generally perceived as related to a **delayed presentation to care**. Nevertheless, data from resource-limited settings suggests its **growing prevalence among ART-experienced PWH**, raising an emerging issue in the HIV continuum of care
- Data comparing the **clinical/epidemiological profiles** and **outcomes** of PLWH with **AHD** who present late to care versus those who are ART-experienced are scarce

Burden of AHD in ART-experienced PWH

Clinical Infectious Diseases

SUPPLEMENT ARTICLE



High Proportions of Patients With Advanced HIV Are Antiretroviral Therapy Experienced: Hospitalization Outcomes From 2 Sub-Saharan African Sites

Janet Ousley,¹ Aline Aurore Niyibizi,¹ Stephen Wanjala,¹ Alexandra Vandenbulcke,¹ Beatrice Kirubi,¹ Willis Omwoyo,¹ Janthimala Price,¹ Leon Salumu,¹ Elisabeth Szumilin,¹ Sofie Spiers,² Gilles van Cutsem,² Maria Mashako,² Freddy Mangana,² Ramzia Moudarichirou,² Rebecca Harrison,² Tony Kalwangila,² Gisele Lumowo,² Vincent Lambert,² and David Maman³

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Comparison of two cohorts of patients presenting with AIDS: patients with previously known HIV diagnoses and true late presenters

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Burden of advanced HIV disease among antiretroviral therapy-experienced persons with HIV in Italy over the past 20 years

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High Proportions of Patients With Advanced HIV Are Antiretroviral Therapy Experienced: Hospitalization Outcomes From 2 Sub-Saharan African Sites

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- Among 338 hospitalized PWH in **Kenya** and 411 in **Congo (DRC)**, 83.7% and 97.3% were admitted with AHD (defined as CD4 <200 cells/μL or World Health Organization stage 3/4 illness)
- Among inpatients with **AHD**, the **majority** (64.7% and 78.2%) **were ART-experienced** at admission
- Many hospitalized patients were in **clinical, immunological, or virological failure**
 - Kenya: 80.5% clinical (WHO stage 3/4), 45.8% immunological, 63.2% virological
 - DRC: 97.0% clinical, 53.4% immunological, 62.0% virological

Table 2. Primary Comorbidities at Admission and Case Fatality Rates Among Antiretroviral Therapy (ART)–Naïve and ART-Experienced Human Immunodeficiency Virus–Infected Inpatients

Comorbidity	Kenya (n = 338)						DRC (n = 376)					
	Late Presenters ^a			ART Experienced			Late Presenters ^a			ART Experienced		
	ART-Naïve	CFR	ART <6 mo	CFR	ART >6 mo	CFR	ART-Naïve	CFR	ART <6 mo	CFR	ART >6 mo	CFR
Tuberculosis	20 (17.1)	25.0	21 (33.9)	28.6	38 (24.5)	26.3	55 (67.1)	30.9	63 (76.8)	45.9	134 (63.2)	25.0
CCM	6 (5.1)	50.0	8 (13.6)	25.0	10 (6.5)	20.0	8 (9.8)	12.5	8 (9.8)	37.5	21 (9.9)	9.5
PCP	0	NA	0	NA	0	NA	5 (6.1)	60.0	7 (8.5)	50.0	13 (6.1)	46.2
Malaria	25 (21.4)	0	6 (10.2)	33.3	23 (14.8)	4.4	12 (14.6)	27.3	14 (28.6)	28.6	34 (16.0)	23.5
Toxoplasmosis	2 (1.7)	0	0	NA	1 (0.6)	0	19 (23.2)	36.8	19 (23.2)	38.9	28 (13.2)	46.4
Kaposi sarcoma	0	...	2 (1.7)	0	6 (3.9)	33.3	2 (2.4)	50	2 (2.4)	50	4 (1.9)	75.0
Gastroenteritis	21 (17.9)	19.1	10 (16.9)	10.0	25 (16.1)	4.0	...	...	...	...	...	...
Bacterial meningitis	11 (9.4)	27.3	6 (10.2)	83.3	12 (9.4)	25.0	...	...	...	...	...	...

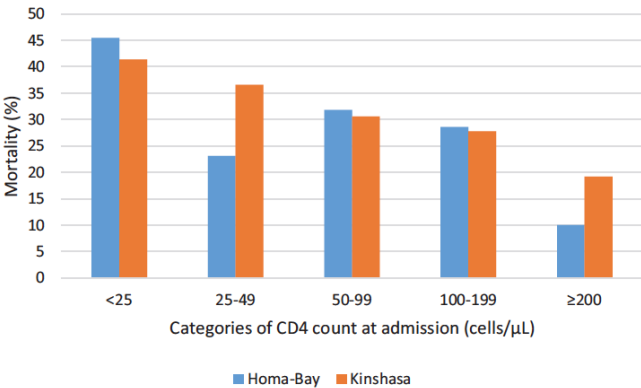


Figure 1. Mortality among patients diagnosed with tuberculosis, stratified by CD4 cell count at admission, Homa-Bay, Kenya (n = 80) and Kinshasa, Democratic Republic of Congo (n = 248).

Comparison of two cohorts of patients presenting with AIDS: patients with previously known HIV diagnoses and true late presenters

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A retrospective analysis of all inpatients admitted to a large HIV unit (in UK) presenting with the following **AIDS-defining infections**: cryptococcal meningitis, cerebral toxoplasmosis or *Pneumocystis jirovecii* pneumonia between 1 January 2005 and 31 December 2010

Table 1 Differences between post-HIV diagnosis AIDS patients (PHDA patients) and late presenters

	PHDA patients (n=54)	Percentage or IQR	Late presenters (n=47)	Percentage or IQR	p Value
Patient characteristics					
Median age	40	36–44	40	33.5–45	0.764
Gender					
Male	43	79.6	41	87.2	0.308
Ethnicity					
Caucasian	32	59.3	32	68.1	0.477
Non-Caucasian	22	40.7	15	31.9	
Migrant or visitor	29	53.7	16	34.0	0.047
HIV risk factors					
MSM	36	66.7	26	55.3	0.243
Intravenous drug user	5	9.3	0	0	0.032
Others	4	7.4	4	8.5	0.564
Unknown	10	18.5	17	36.2	
Previous clinical indicator disease	31	57.4	6	12.8	0.000
Previous chemoprophylaxis	13	24.1	0	0	0.005
Psychiatric comorbidities	19	35.2	6	12.8	0.009
Alcohol abuse	13	24.1	2	4.3	0.005
Substance abuse	12	22.2	1	2.1	0.003
Social Issues	14	25.9	0	0	0.000
Median time from diagnosis to AIDS (years)	7.3	4.0–13.3	0	0–0	
Median CD4 at diagnosis (cells/microlitre)	263	125–430	43	10.5–184.0	
Median Viral load at diagnosis (copies/ml)	45632	16384–165750	202747	77356–188474	
Median LTFU period (months)	11	6–19			

Key messages

- ▶ Half of the patients presenting with AIDS-defining illnesses have previously diagnosed HIV infections (post-HIV diagnosis AIDS patients).
- ▶ These patients have higher rates of psychiatric comorbidities, social issues and alcohol and substance abuse.
- ▶ These patients often have treatment breaks and clinic non-attendance due to potentially modifiable factors such as social issues, drug side effects and treatment avoidance.

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Burden of advanced HIV disease among antiretroviral therapy-experienced persons with HIV in Italy over the past 20 years

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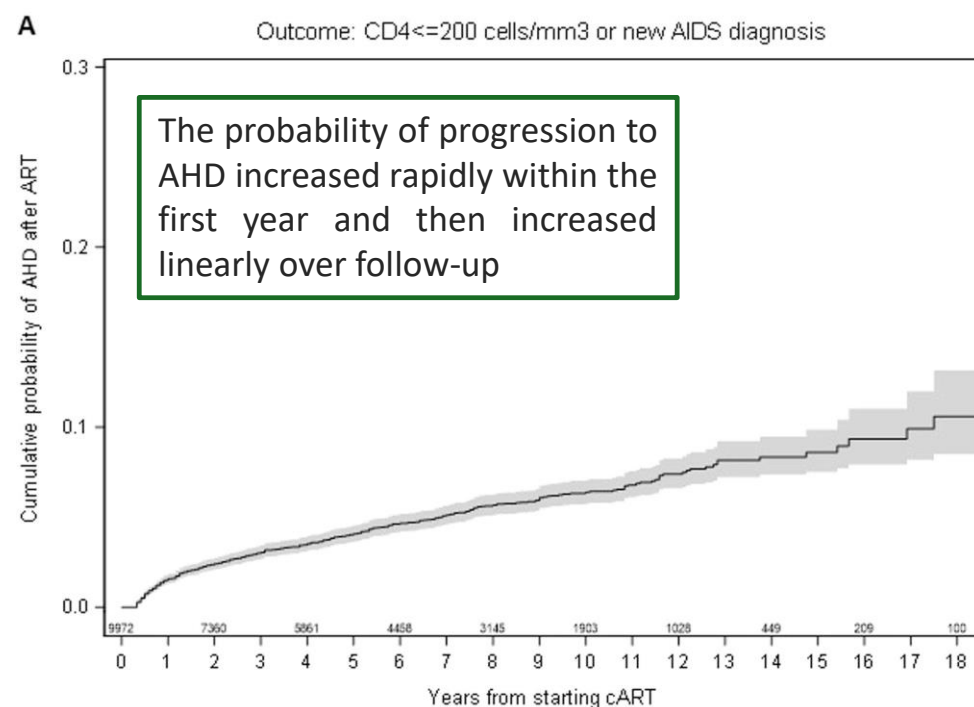
- **Study population:** all **PWH** enrolled in the ICONA cohort who **started ART** between January 1st, 2004, and July 31st, 2024 with a **pre-treatment CD4 count ≥ 200 cells/mm³** and **no prior AIDS-defining events (ADE)**
- The data of the **whole cohort** were used to estimate the **incidence of AHD** (defined as a CD4 cell count < 200 cells/mm³ or an ADE, regardless of CD4 count, occurring more than three months after ART initiation)
- To address the second aim of identifying time-varying **factors associated with the risk of AHD**, a **nested-case control study** within the identified cohort was performed. AHD cases were matched 1:2 to controls by CD4 *nadir*, age, and ART duration.

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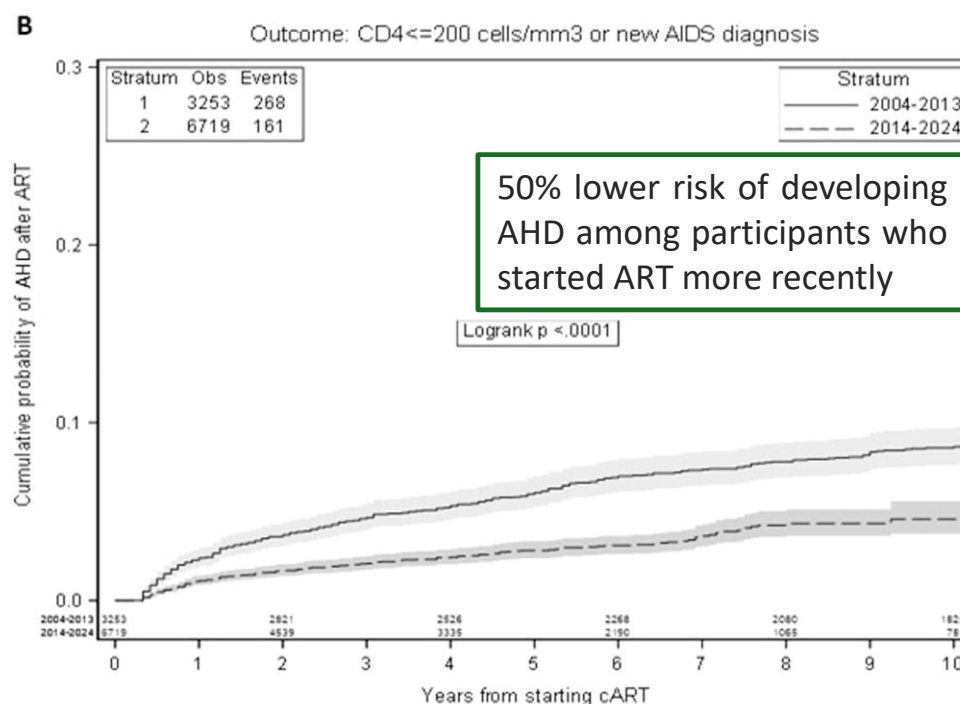
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- **9,972** PWH without AHD at ART initiation included in the analysis
- Over a five-year median follow-up, **429 individuals (4.3%) developed AHD** at least three months after starting ART:
 - **111 (26%) ADE:** non-Hodgkin lymphoma (22.5%), Kaposi's sarcoma (19.8%), tuberculosis (18.9%), esophageal candidiasis (10.8%), and atypical mycobacterial disease (4.5%)
 - **318 (74%) CD4 decline < 200 cells/mm³**



95% Confidence Limits



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Factors associated with the risk of AHD

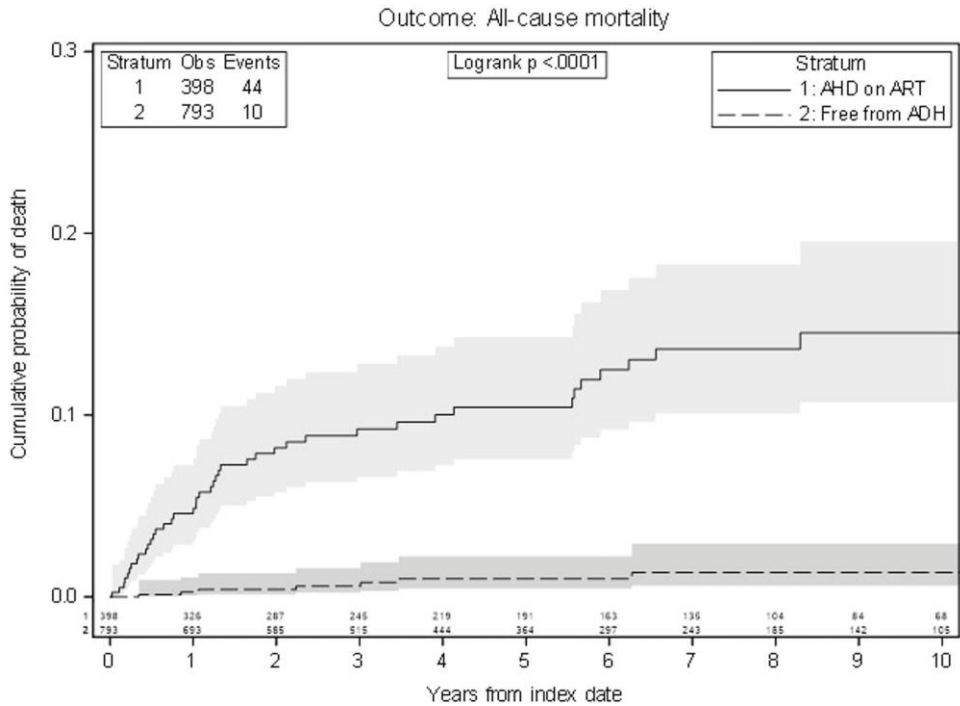
In the nested case-control study, 424 of the 429 participants who developed AHD were matched with 844 controls, resulting in total of 1,268 PWH

- Cisgender female sex
- Lower education
- Unemployment
- HIV acquisition via injection drug use
- History of prolonged (>18 months) disengagement from care
- Suboptimal virologic control (defined as either failure to achieve virologic suppression since ART initiation or incomplete virologic suppression within the prior year)
- Multi-tablet ART regimen (MTR)

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By ten years, **mortality risk** was significantly **higher** among participants with **AHD** compared to those who were free from AHD with the highest excess risk in the **first two years after AHD diagnosis**

Mortality in ART-experienced PWH with AHD

	UNADJUSTED HR	P-VALUE	ADJUSTED* HR	P-VALUE
Not-AHD (not-exposed)	1		1	
AHD (exposed)	8.74 (4.40, 17.37)	<0.001	8.58 (4.29, 17.19)	<0.001

Table 3
Unadjusted and adjusted relative hazards of all-cause mortality in subjects with AHD (exposed) versus not-exposed by fitting a cox regression model.

Abbreviations: HR, hazard ratio; AHD, advanced HIV disease; **Notes:** adjusted for age, gender, nationality, mode of HIV transmission, year of AHD/index time, and hepatitis co-infection

Comparison between AHD-naïve e AHD-experienced PWH

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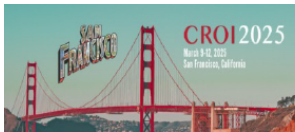
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Differences in Mortality Between Treatment-Naive and Treatment-Discontinuing Hospitalized Individuals With Advanced Human Immunodeficiency Virus Disease: A Comparative Retrospective Study From Mexico City

Héctor Rivera-Villegas,[●] Yanink Caro-Vega, André Trujillo-Gamboa,[●] Álvaro Lopez-Iñiguez,[●] Juan Sierra-Madero, and Brenda Crabtree-Ramirez[●]

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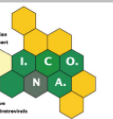


Advanced HIV Disease in individuals already in care: incidence and comparison with late presentation

Annalisa Mondì¹, Ashley Roen², Alessandro Cozzi-Leperi², Andrea Giacomelli³, Annalisa Saracino⁴, Antonio Di Biagio⁵, Carlo Torti⁶, Davide Checchi⁷, Massimo Puoti⁸, Eugenia Quiros-Roldan⁹, Silvia Nozza¹⁰, Sergio Lo Caputo¹¹, Enrico Girardi¹, **Andrea Antinori¹** on behalf of Icona Foundation Study Group.

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1133



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Differences in Mortality Between Treatment-Naive and Treatment-Discontinuing Hospitalized Individuals With Advanced Human Immunodeficiency Virus Disease: A Comparative Retrospective Study From Mexico City

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Table 1. Demographic and Clinical Characteristics at First Hospitalization

Variable	Total (n = 299)	Treatment Naive (n = 214 [72%])	Treatment Discontinued (n = 85 [28%])	P Value
Male sex, No. (%)	261 (87)	189 (88)	72 (85)	.513
Age, y, median (IQR)	37 (30–45)	36 (30–46.75)	37 (30–44)	.807
Education, y, median (IQR)	13 (9–15)	14 (9–15)	12 (9–12)	.079
HIV sexual transmission ^a , No. (%)	264 (88)	191 (90)	73 (86)	.009
Comorbidities ^b , No. (%)	90 (30)	59 (28)	31 (36)	.169
Hospitalization days ^c , median (IQR)	10 (5–18)	10 (5–14.6)	9 (4–13.6)	.502
CD4 count ^d , cells/μL, median (IQR)	44 (16–106)	46.5 (17–106)	40 (14–106)	.735

- Retrospective cohort study at a tertiary care referral center located in Mexico City, Mexico (January 2015–December 2022) including individuals aged ≥18 years hospitalized for AHD-related complications
- **Study population**
 - treatment- naive individuals → those with AHD who have never taken ART
 - treatment-discontinuing individuals → those with a history of ART initiation and loss to follow-up with ART discontinuation for >6 months

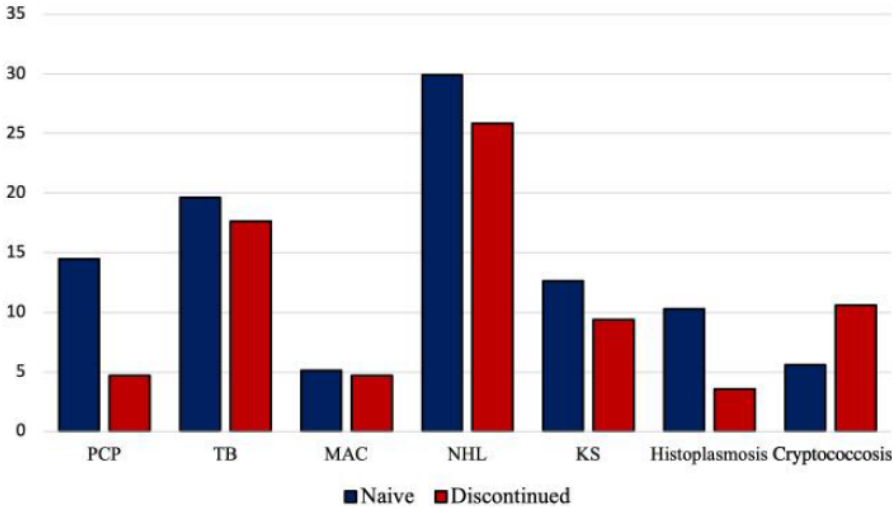


Figure 2. Percentage of AIDS-defining events at hospitalization. Abbreviations: KS, Kaposi sarcoma; MAC, *Mycobacterium avium* complex infection; NHL, non-Hodgkin lymphoma; PCP, *Pneumocystis jirovecii* pneumonia; TB, tuberculosis.

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Table 3. Multivariate Analysis for Primary Outcome

Variable	aHR (95% CI)	P Value
Treatment group		
Naive	1	.016
Discontinued	2.08 (1.14–3.78)	
Sex at birth		
Male	1	.832
Female	0.90 (.13–2.32)	
Age, y		
25	1	.38
45	1.79 (.96–4.63)	
50	1.83 (.74–4.53)	
CD4 count, cells/ μ L		
50	1	.86
200	0.70 (.35–1.38)	
350	0.49 (.12–1.91)	
HIV acquisition risk		
Nonsexual	1	.62
Sexual	0.77 (.27–2.19)	
Comorbidities		
No	1	.99
Yes	1.00 (.55–1.82)	
No. of hospitalizations		
1	1	.30
≥ 2	0.34 (.27–2.18)	

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HIV, human immunodeficiency virus.

Table 2. Mortality Outcomes

Variable	Total (n = 299)	Treatment Naive (n = 214 [72%])	Treatment Discontinued (n = 85 [28%])	P Value
1-y mortality	47 (16)	24 (11)	23 (27)	.008
Overall mortality	48 (16)	25 (12)	23 (27)	.008
30-d mortality	38 (13)	18 (8)	20 (24)	.062
Cause of death				
Infections	33 (69)	71	16	.504
Cancer	15 (31)	10	5	

Data are presented as No. (%) unless otherwise indicated.

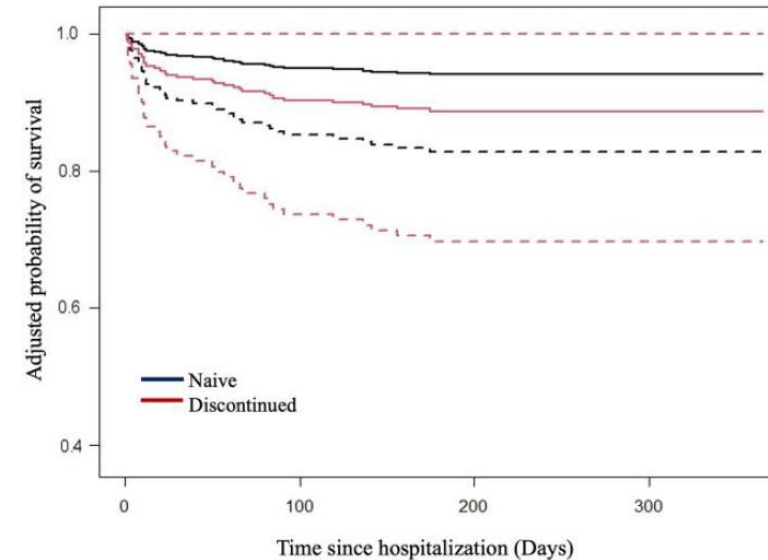


Figure 3. One-year adjusted survival according to treatment-naive and treatment-discontinued groups. Predicted survival curves are for 45-year-old men with comorbidities reported, who had a CD4⁺ count of 50 cells/ μ L, human immunodeficiency virus acquisition risk of sexual contact, and 2 or more hospitalization events.

Advanced HIV Disease in individuals already in care: incidence and comparison with late presentation

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Table 1: Participants 'characteristics at AHD diagnosis by exposure group

	PREVALENT AHD [n=4,799, 86%]	INCIDENT AHD [n=788, 14%]	TOTAL [n=5,587]	p-value
FEMALE GENDER, n (%)	1,092 (22.8%)	228 (28.9%)	1,320 (23.6%)	0.001
AGE, YEARS, median (IQR)	43 (35-52)	44 (37-51)	43 (36-52)	0.002
MODE OF HIV TRANSMISSION, n (%)				<0.001
Homosexual	1,524 (31.8%)	255 (32.4%)	1,779 (31.8%)	
Heterosexual	2,455 (51.2%)	316 (40.1%)	2,771 (49.6%)	
People who inject drugs	371 (7.7%)	177 (22.5%)	548 (9.8%)	
NOT ITALIAN NATIONALITY, n (%)	1,350 (28.1%)	126 (16.0%)	1,476 (26.4%)	<0.001
CD4 COUNT AT AHD, cells/mm³, median (IQR)	124 (71-165)	159 (109-185)	131 (77-170)	<0.001
HIV-RNA AT AHD, log₁₀ copies/mL, median (IQR)	5.31 (4.78-5.79)	2.08 (1.40-4.67)	5.17 (4.44-5.70)	<0.001
AIDS-defining event, n (%)	1,628 (33.9%)	269 (34.1%)	1897 (34.0%)	0.907
FIRST-LINE ART, n (%)				
- PI-based	1,686 (35.1%)	263 (33.4%)	1,949 (34.9%)	0.022
- NNRTI-based	562 (11.7%)	223 (28.3%)	785 (14.1%)	<0.001
- INSTI-based	1,941 (40.4%)	113 (14.3%)	2,054 (36.8%)	<0.001
COMORBIDITIES				
- Cardiovascular	55 (1.1%)	15 (1.9%)	70 (1.3%)	0.076
- Diabetes	124 (2.6%)	49 (6.2%)	173 (3.1%)	<0.001
- Hypertension	201 (4.2%)	84 (10.7%)	285 (5.1%)	<0.001
- Hepatitis co-infection	288 (6.1%)	228 (28.9%)	516 (9.2%)	<0.001
ALCHOL ABUSE (%)	79 (1.5%)	62 (7.9%)	141 (2.4%)	<0.001
SMOKING, n (%)	937 (19.5%)	328 (41.6%)	1,265 (22.6%)	<0.001
EDUCATION LEVEL, n (%)				<0.001
- Primary School	317 (6.6%)	64 (8.1%)	381 (6.8%)	
- Secondary School	2,139 (44.6%)	459 (58.2%)	2,598 (46.5%)	
- College/University	421 (8.7%)	53 (6.7%)	474 (8.4%)	
EMPLOYMENT STATUS, n (%)				<0.001
- Unemployed	660 (13.7%)	121 (15.3%)	781 (14.0%)	
- Employed/self-employed	2,493 (51.9%)	470 (59.6%)	2,963 (53.0%)	
- Student/occasional	205 (4.3%)	40 (5.1%)	245 (4.4%)	
- Retired/Housewife	339 (7.0%)	56 (7.1%)	408 (7.1%)	

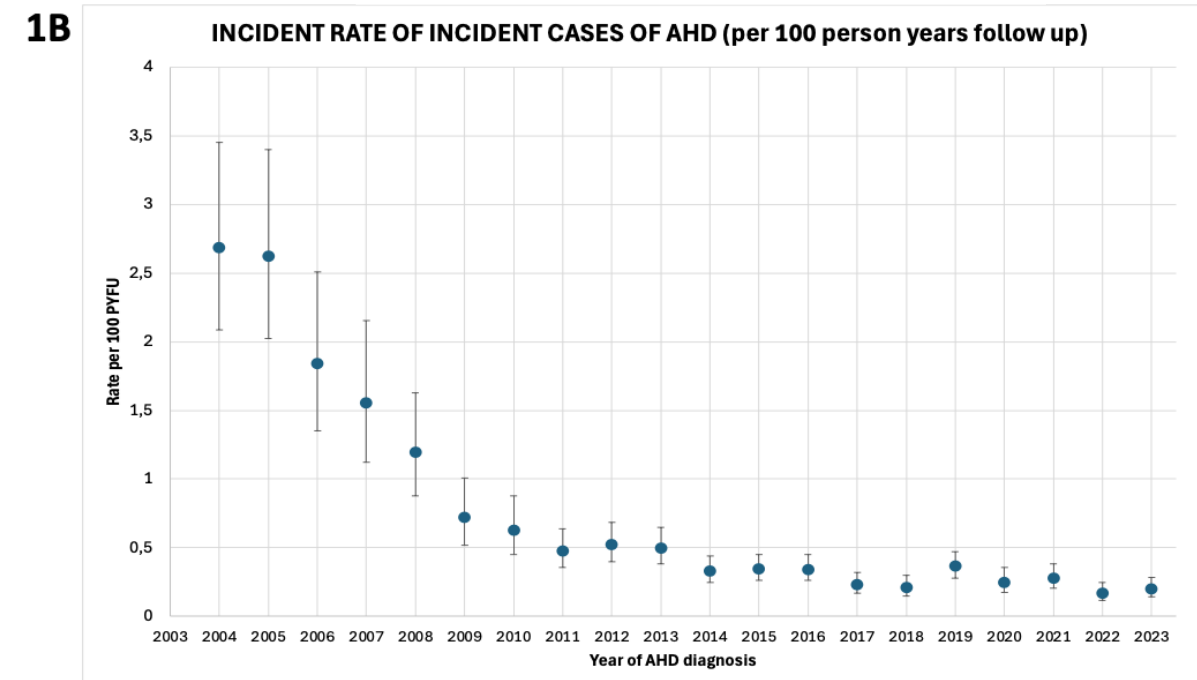
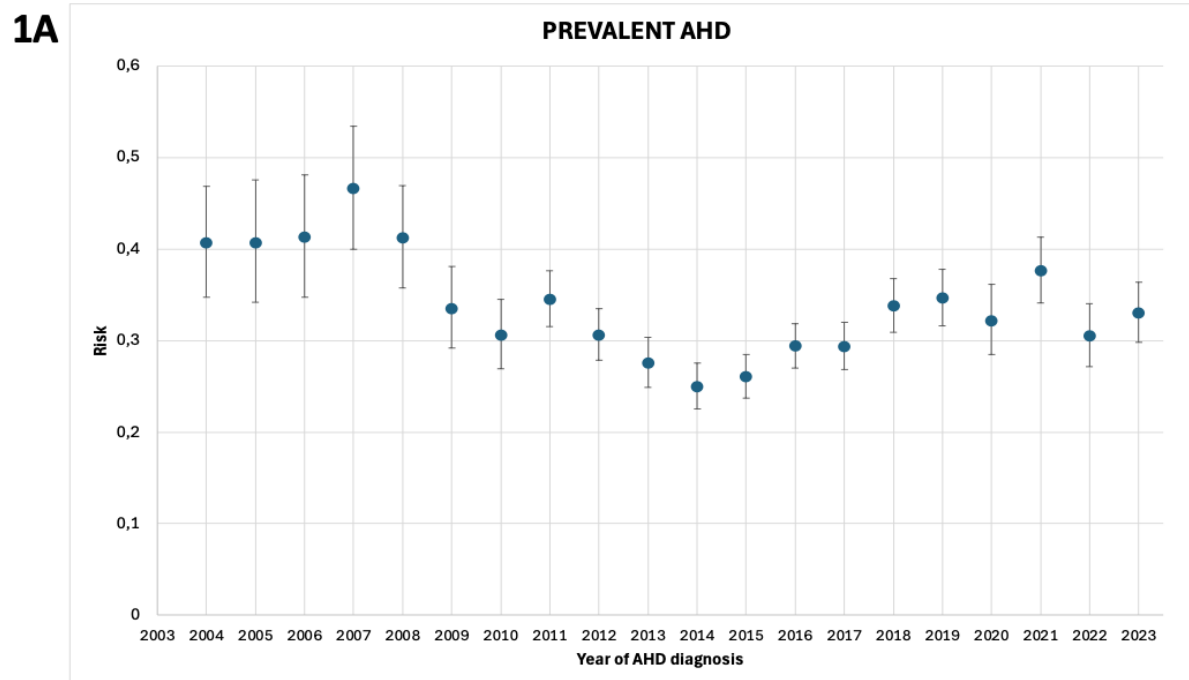
POPULATION: All PWH, enrolled in the **Icona Foundation Study Cohort**, who received a **first diagnosis of AHD** [CD4 count <200 cell/mm³ or AIDS-defining event (ADE), regardless of CD4 count] between **Jan 2004 and Dec 2024** were included. Participants were categorized into: **1) Prevalent AHD (pAHD)** [AHD diagnosed at the time of HIV diagnosis] and **2) Incident AHD (iAHD)** [AHD diagnosed >3 months after ART starting]. Groups were further stratified by the presence of ADE.

Advanced HIV Disease in individuals already in care: incidence and comparison with late presentation

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Figure 1: Annual trends in pAHD risk (1A), iAHD incidence rate (1B)

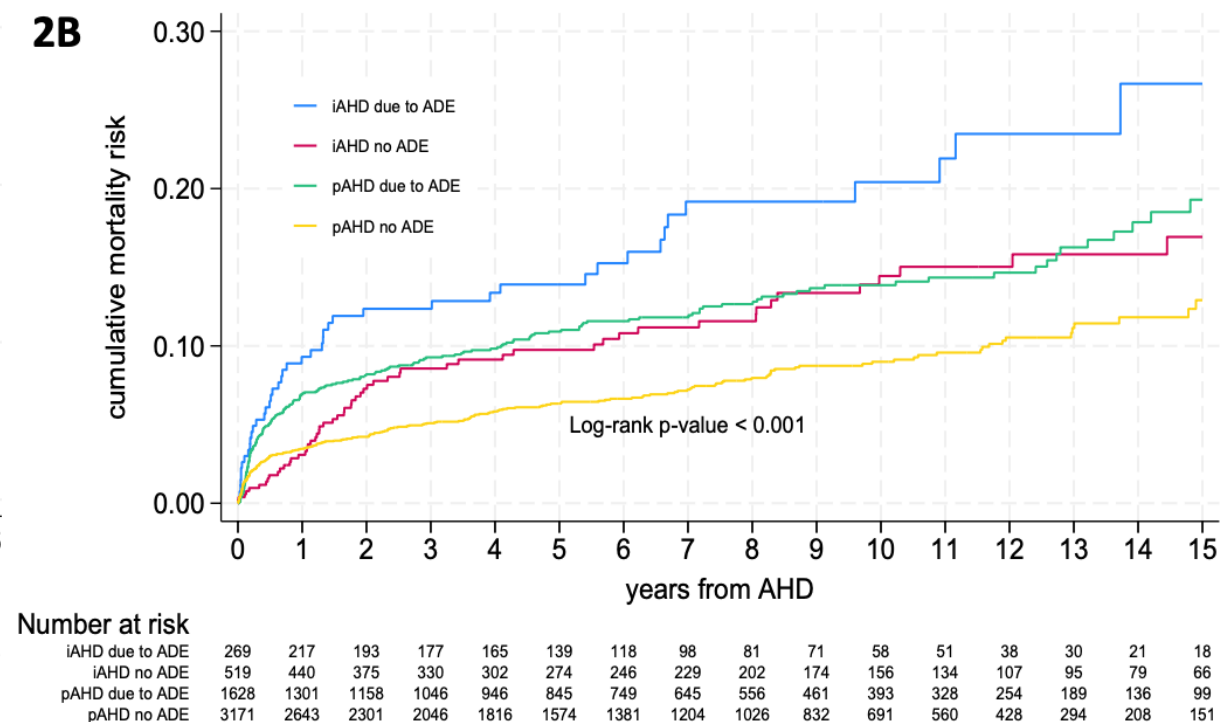
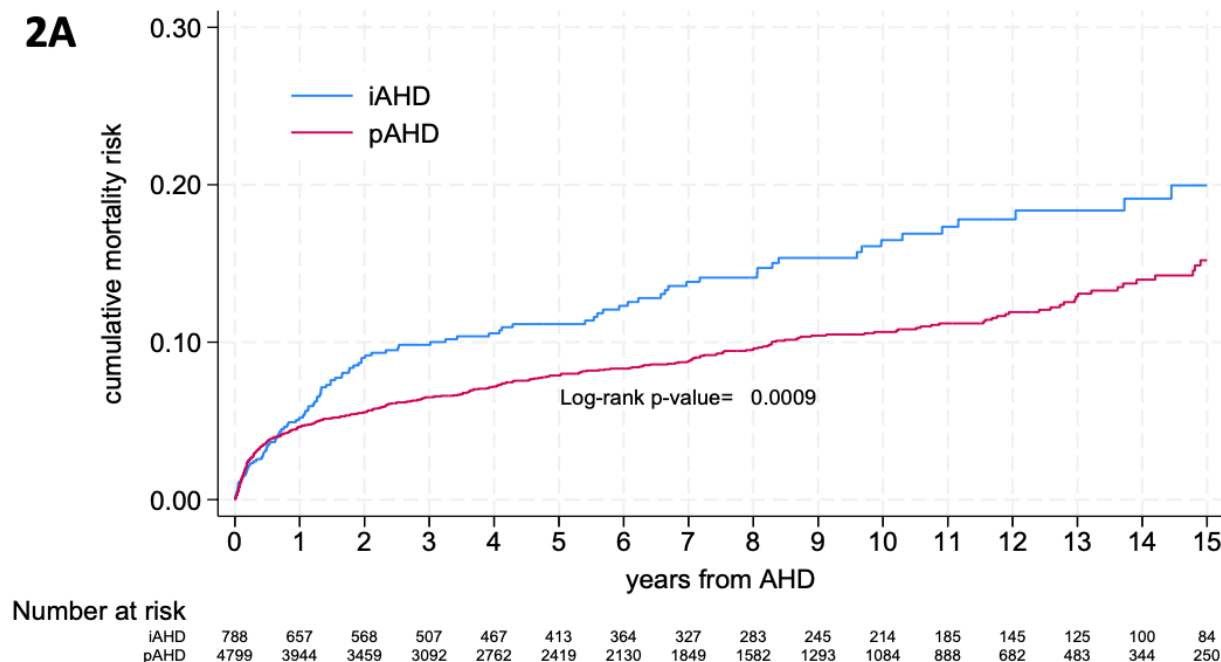


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Figure 2: Probability of all-cause mortality by exposure group (2A) and after stratification by ADE (2B)

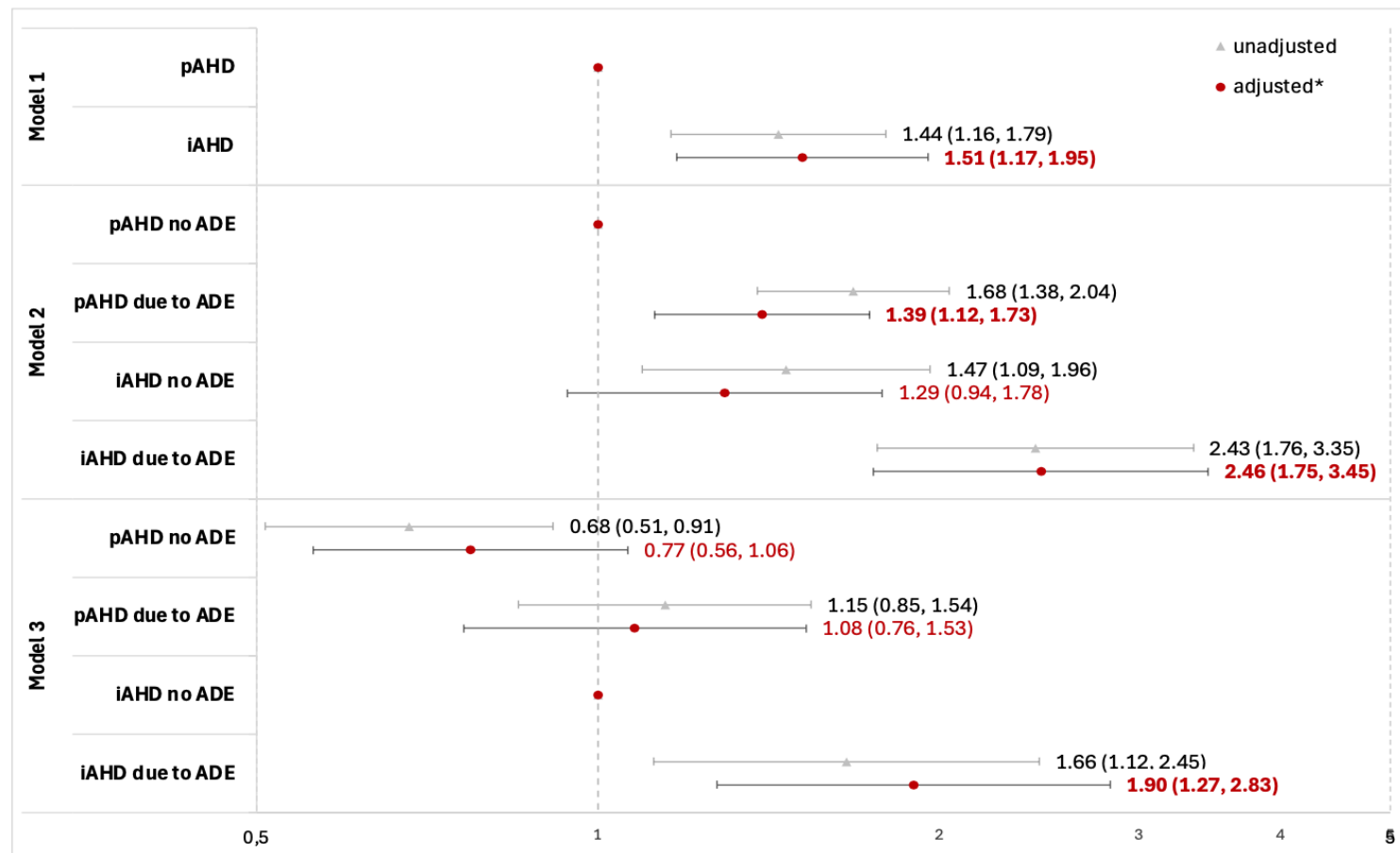


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Figure 3: Hazard ratios of all-cause mortality from fitting Cox regression models



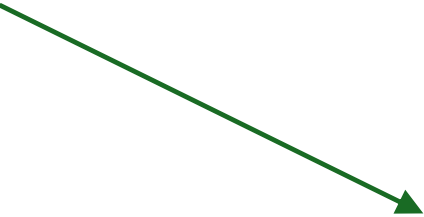
* **Confounders for adjusted models:** age, comorbidities (one at a time), CD4 count, smoking/alcohol, employment, sex at birth HIV transmission risk factor, calendar year of AHD diagnosis, education, nationality, third drug. **Significant p-values are shown in bold.**

Conclusions (I)

- ART-experienced individuals who develop **AHD** are more likely to exhibit signs of **social disadvantage** compared to those who do not progress. Specifically, these individuals are more likely to have a history of **injecting drug use, smoking** and a **lower socio-economic status** (unemployment and lower levels of education)
- Risk of **progression to AHD** is **higher** in **women**
- **Suboptimal virologic control** and **prolonged disengagement from care** play a key role in the development of AHD

Conclusions (II)

- **Higher mortality** in **ART-experienced PWH with AHD** compared to ART-naïve PWH
- **Mechanisms** underlying this **mortality gap** are currently **unknown**
 - socio-demographic factors?
 - viro-immunologic factors?



A prior study by Thomadakis *et al.* (*AJE* 2023) reported a **slower CD4 T cell recovery upon ART reinitiation after a period of discontinuation**, suggesting that **ART interruption may be associated with an alteration of the immune system homeostasis**, potentially leading to increased morbidity/mortality