Benefits of Antiretroviral Therapy

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Kyiv 8 June 2018

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Objectives:

- Understanding the individual benefits of antiretroviral therapy

- Identify the benefit of antiretroviral therapy on a population level

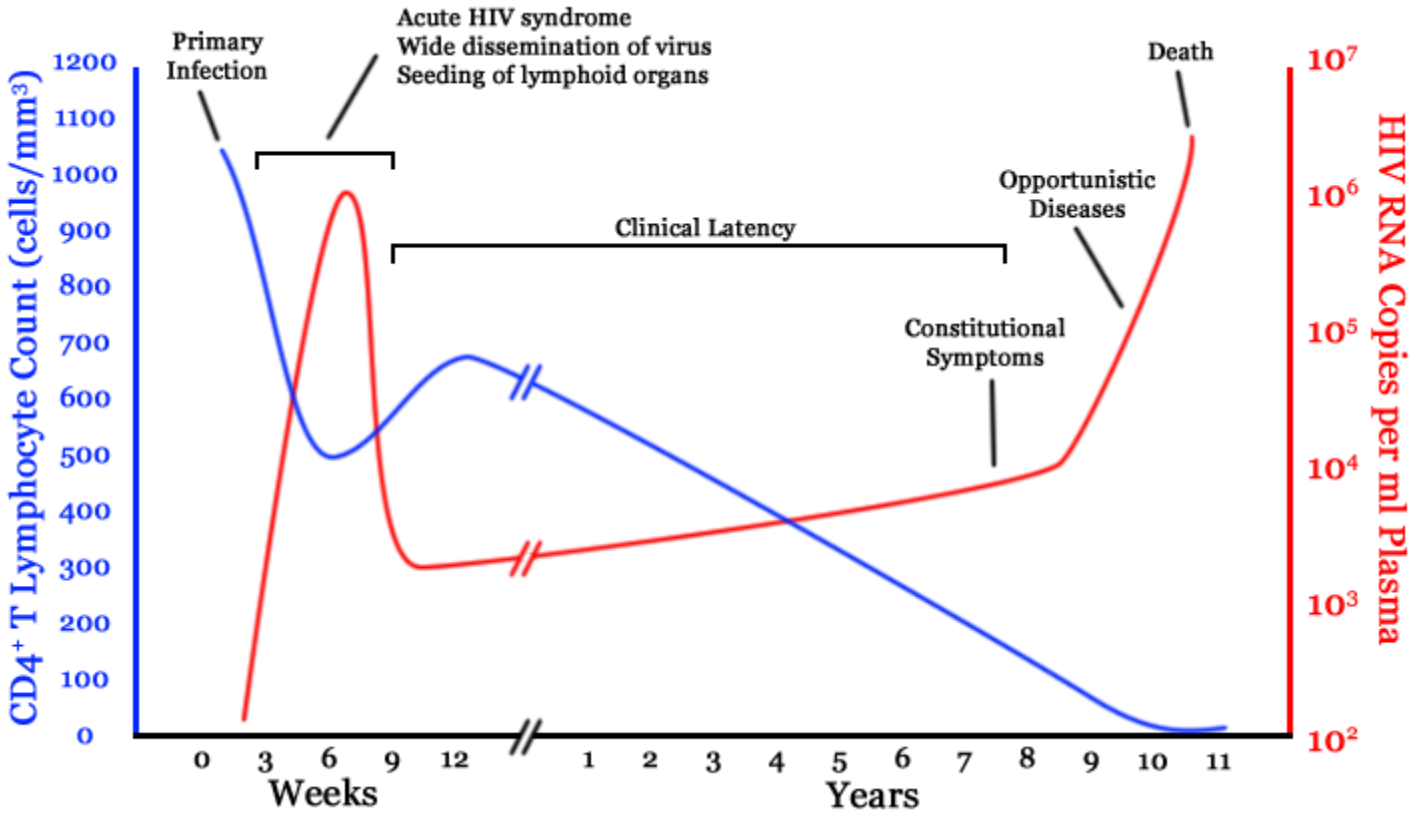
1981-1996

No highly active antiretroviral therapy (HAART)/combination antiretroviral therapy (cART)

HIV: incubation period (= latency period, asymptomatic phase) from HIV infection to AIDS ~10 years

AIDS: median survival time 10-13 months (with opportunistic infections ~9 months, with Kaposi Sarcoma ~13 months)

http://hivinsite.ucsf.edu/InSite?page=kb-03-01-04#S2X



Fauci Ann Intern Med. 1996;124(7):654-663
http://annals.org/aim/fullarticle/709558/immunopathogenic-mechanisms-hiv-infection

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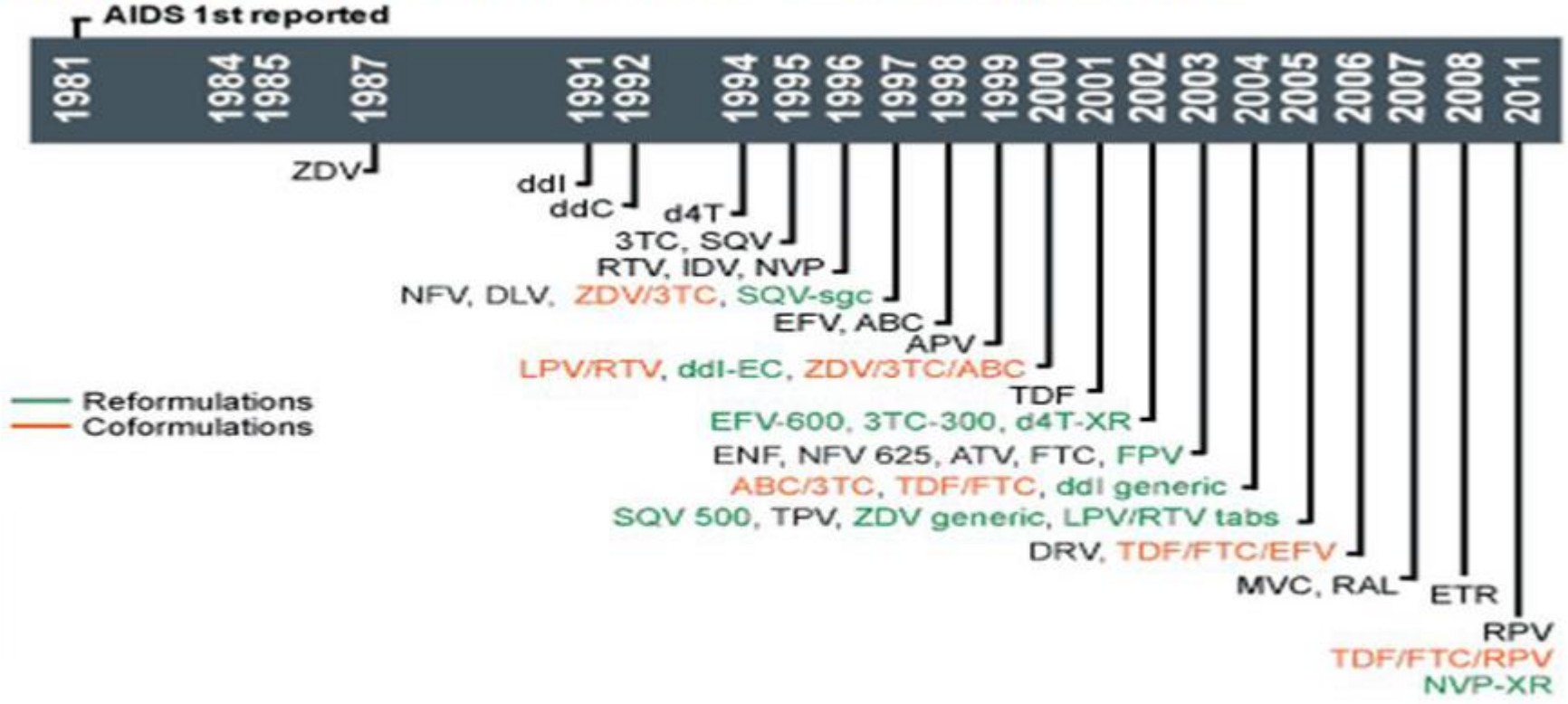
Figure 1. Timeline for development of antiretroviral agents.



3TC, lamivudine; ABC, abacavir; APV, amprenavir; ATV, atazanavir; d4T, stavudine; ddC, zalcitabine; ddI, didanosine; DLV, delavirdine; DRV, darunavir; EFV, efavirenz, ENF, enfuvirtide; ETR, etravirine; FPV, fosamprenavir; FTC, emtricitabine; IDV, indinavir; LPV, lopinavir; MVC, maraviroc; NFV, nelfinavir; RTV, ritonavir; RAL, raltegravir; RPV, rilpivirine, SQV, saquinavir; TDF, tenofovir; ZDV, zidovudine.

A Mohamed http://slideplayer.com/slide/4375959/

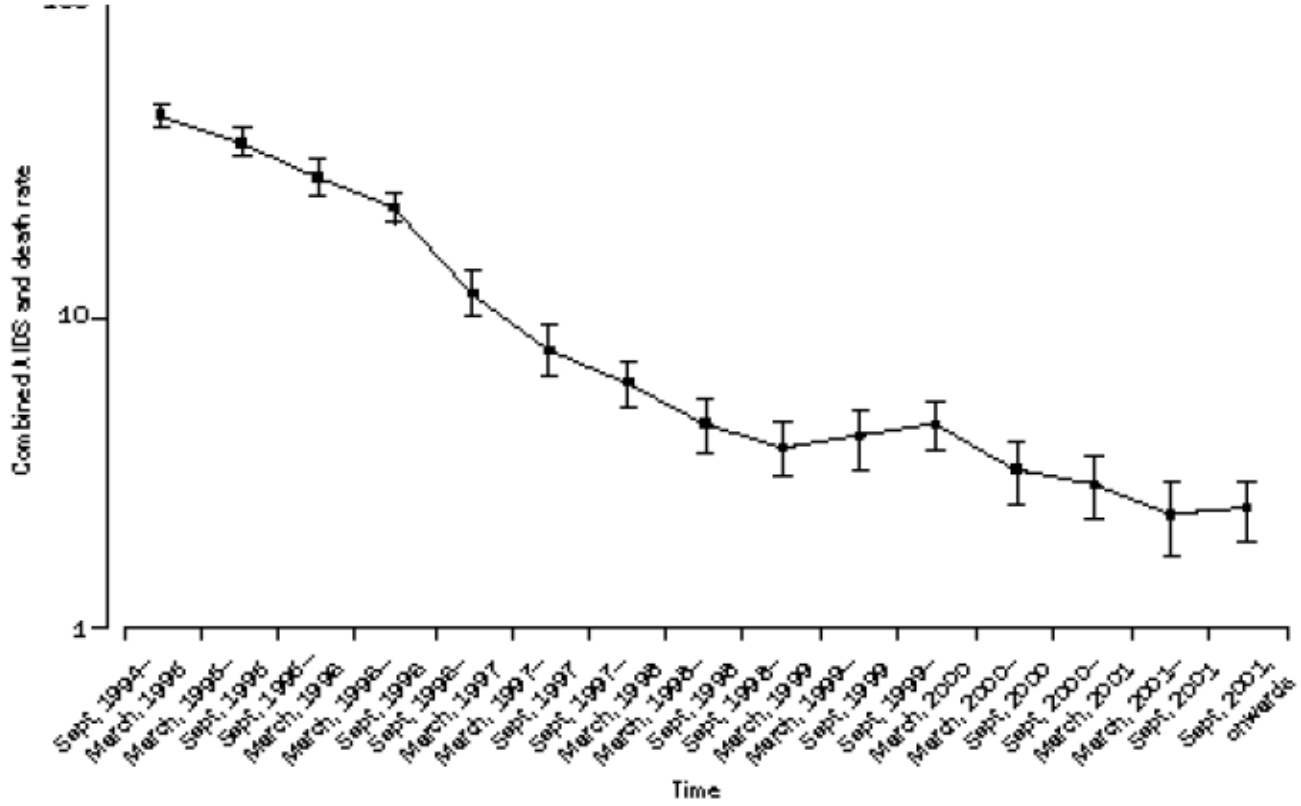
1996ff HAART / cART

Decline of

- AIDS-defining disorders (esp. opportunistic infections and tumors)

- mortality due to AIDS

- overall mortality



	Sept, 1994–March, 1995	March, 1995–Sept, 1995	Sept, 1995–March, 1996	March, 1996–Sept, 1996	Sept, 1996–March, 1997	March, 1997–Sept, 1997	Sept, 1997–March, 1998	March, 1998–Sept, 1998	Sept, 1998–March, 1999	March, 1999–Sept, 1999	Sept, 1999–March, 2000	March, 2000–Sept, 2000	Sept, 2000–March, 2001	March, 2001–Sept, 2001	Sept, 2001 onwards
Events (n)	522	351	227	232	146	87	140	105	84	88	114	80	69	58	73
Median CD4 (cells/μL) at event (IQR)	29 (10–84)	27 (9–100)	30 (10–100)	31 (10–97)	62 (15–161)	89 (35–223)	108 (47–208)	127 (45–344)	149 (40–285)	100 (25–222)	125 (40–266)	150 (30–318)	187 (80–303)	220 (107–402)	220 (90–397)

Figure 2: **Combined AIDS and death rates**
Vertical bars=95% CIs.

Latest CD4	Pre-HAART (95% CI)	Early-HAART (95% CI)	Late-HAART (95% CI)	Test for trend p value*	Test for trend p value†
All deaths					
Latest CD4 (cells μL)					
⩽20	68·9 (62·8–75·0)	80·0 (71·5–88·5)	34·6 (28·6–40·6)	<0·0001	<0·0001
21–50	32·2 (26·9–37·5)	28·1 (22·7–33·5)	25·7 (20·5–30·9)	0·0083	0·52
51–100	21·1 (16·7–25·5)	9·5 (7·1–11·9)	8·3 (6·3–10·3)	<0·0001	0·44
101–200	5·9 (4·2–7·6)	4·0 (3·0–5·0)	4·0 (3·3–4·7)	0·046	0·95
201–350	2·7 (1·7–3·7)	1·4 (0·9–1·5)	1·4 (1·1–1·7)	0·013	0·89
>350	1·4 (0·6–2·5)	1·2 (0·7–1·8)	0·7 (0·6–0·8)	0·008	0·041
Total	19·0 (17·7–20·3)	9·3 (8·6–10·0)	2·6 (2·4–2·8)	<0·0001	<0·0001
HIV-related deaths					
Latest CD4 (cells μL)					
⩽20	53·8 (48·4–59·2)	66·8 (59·1–74·6)	26·2 (20·9–31·4)	<0·0001	<0·0001
21–50	22·9 (18·4–27·4)	21·6 (16·8–26·3)	11·9 (8·4–15·4)	<0·0001	0·002
51–100	16·0 (12·2–19·9)	7·3 (5·2–9·3)	5·5 (3·9–7·2)	<0·0001	0·19
101–200	4·7 (3·2–6·2)	2·5 (1·7–3·3)	2·2 (1·7–2·8)	<0·0001	0·54
201–350	1·8 (1·1–2·7)	1·2 (0·7–1·7)	0·8 (0·5–1·0)	<0·0001	0·048
>350	0·9 (0·4–2·0)	1·0 (0·5–1·6)	0·4 (0·3–0·5)	<0·0001	<0·0001
Total	14·6 (13·4–15·8)	7·4 (6·8–8·1)	1·5 (1·4–1·7)	<0·0001	<0·0001
AIDS					
Latest CD4 (cells μL)					
⩽20	97·9 (88·6–107·2)	103·2 (91·5–114·9)	50·4 (41·5–59·3)	<0·0001	<0·0001
21–50	64·8 (56·0–73·6)	52·7 (44·2–61·2)	23·4 (18·0–28·8)	<0·0001	<0·0001
51–100	42·4 (35·5–49·3)	24·7 (20·6–28·3)	10·5 (8·1–12·9)	<0·0001	<0·0001
101–200	15·9 (13·0–18·8)	7·6 (6·2–9·0)	4·3 (3·5–5·1)	<0·0001	<0·0001
201–350	6·1 (4·6–7·6)	3·8 (2·9–4·7)	1·5 (1·2–1·8)	<0·0001	<0·0001
>350	3·6 (2·2–5·0)	2·6 (1·8–3·4)	0·7 (0·5–0·9)	<0·0001	<0·0001
Total	27·4 (25·7–29·1)	13·4 (12·5–14·3)	2·6 (2·4–2·8)	<0·0001	<0·0001

PYFU=person-years of follow-up. *Pre-HAART *vs* early-HAART *vs* late-HAART. †Early-HAART *vs* late-HAART.

Table 2: **Incidence per 100 PYFU of AIDS, all deaths, and HIV 1 related deaths according to treatment era and latest CD4 count**

Mocroft et al. EuroSida Lancet 2003; 362: 22–29 DO

COHERE: Collaboration of Observational HIV Epidemiological Research in Europe

- From 1998-2008, the mortality rates of HIV infected adults after initiation of cART were similar to mortality rates in the general population of the same gender and age

- except for persons with IDU or who have been infected via IDU

- occurence of AIDS before initiation of cART resulted in poorer prognosis

COHERE: Collaboration of Observational HIV Epidemiological Research in Europe

→ arguments in favor of an earlier initiation of antiretroviral therapy !

Lewden et al. COHERE Int J Epidemiol 2012;41:433–445
doi:10.1093/ije/dyr164

Strategic Timing of AntiRetroviral Treatment (START) 2015

- large-scale randomised clinical trial that tested whether earlier ART benefitted all people with HIV

- 4685 treatment naive persons enrolled

Strategic Timing of AntiRetroviral Treatment (START) 2015

- CD4 counts were all over 500 cells/mm^3

- study participants were randomised to start ART immediately or have deferred treatment until their CD4 cell count declined to 350 cells/mm^3

Strategic Timing of AntiRetroviral Treatment (START) 2015

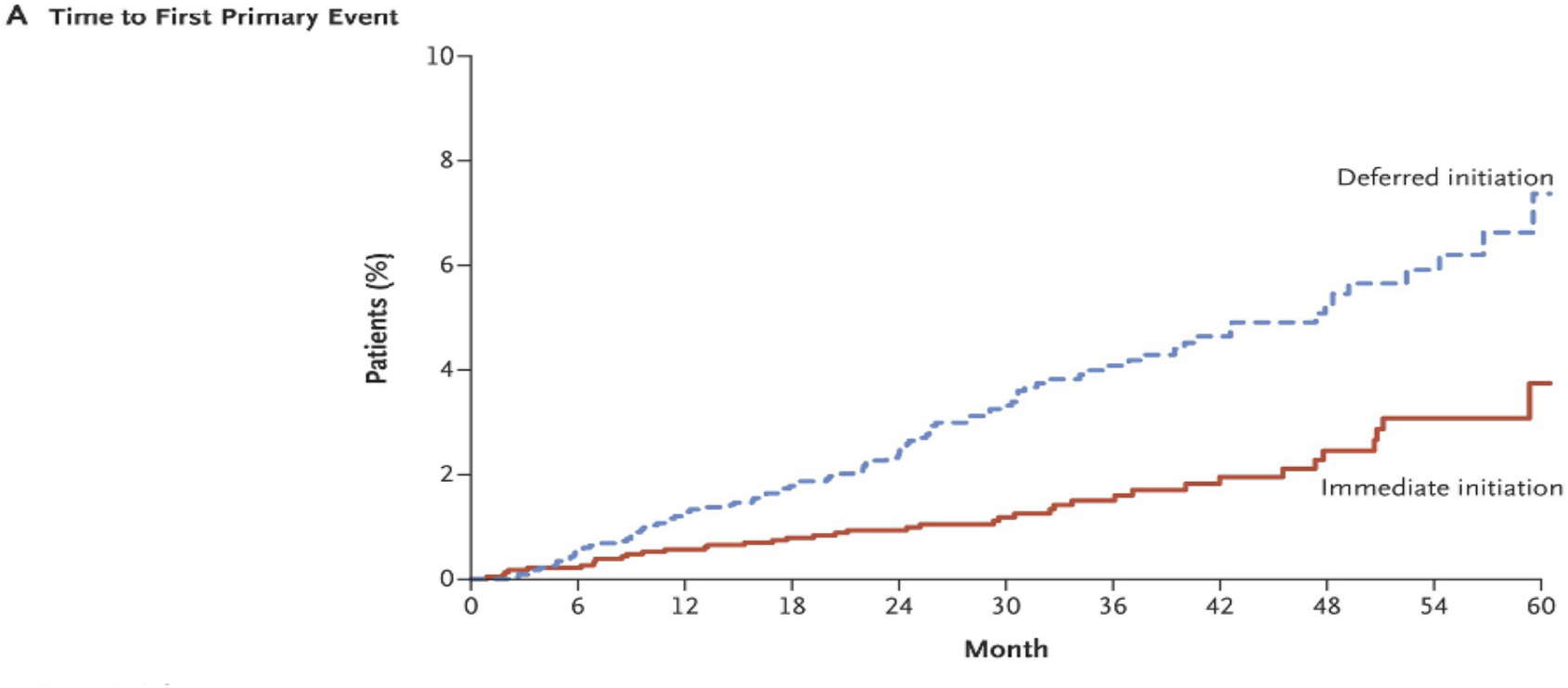
- outcomes measured included serious AIDS events (such as AIDS-related cancer), serious non-AIDS events (major cardiovascular, renal and liver disease and cancer), and death

- 41 instances of AIDS, serious non-AIDS events or death among those enrolled in the group starting ART early, compared to 86 events in those deferring it

http://www.aidsmap.com/START-trial-finds-that-early-treatment-improves-outcomes-for-people-with-HIV/page/2972157/

http://www.nejm.org/doi/full/10.1056/NEJMoa1506816

Strategic Timing of AntiRetroviral Treatment (START) 2015



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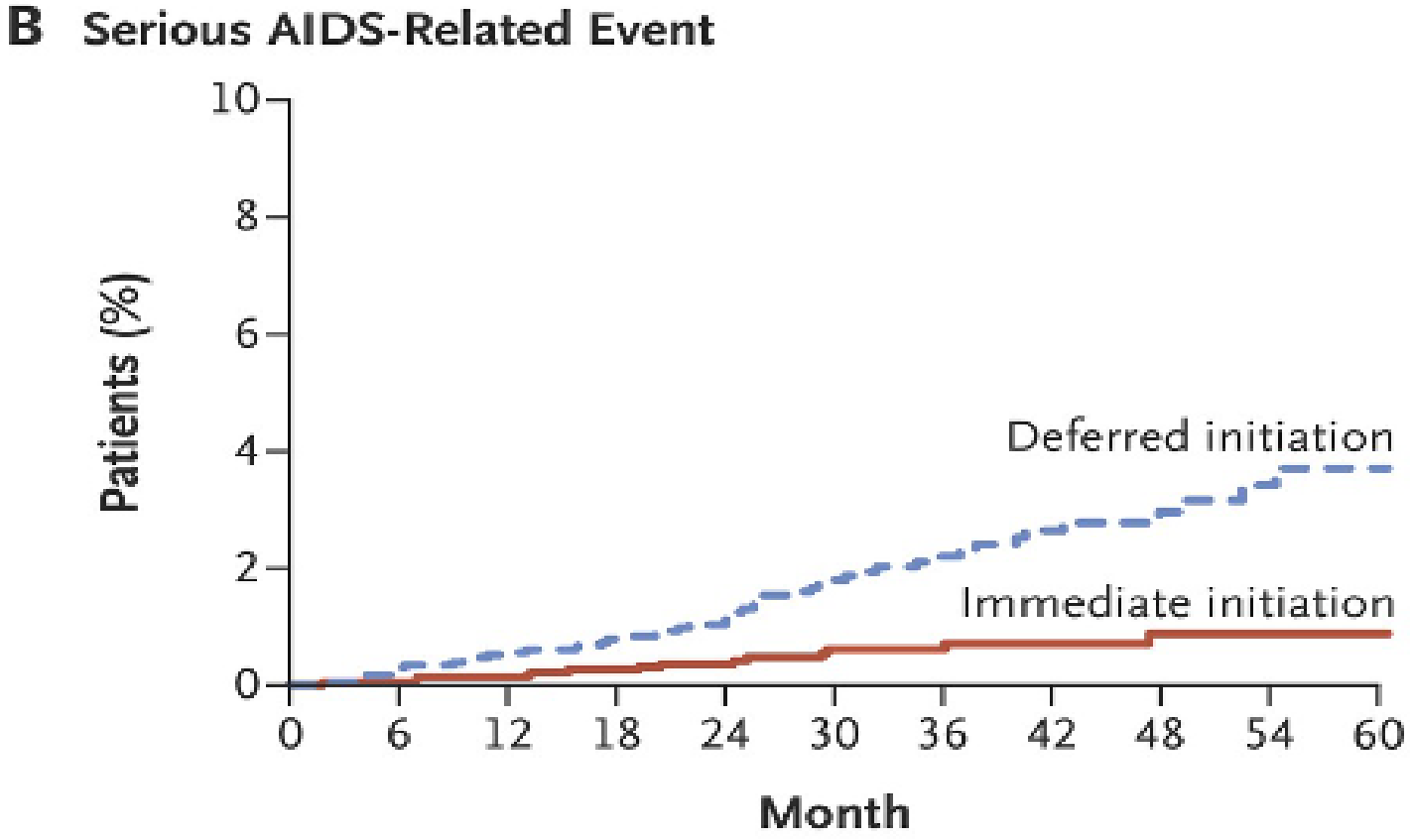
Strategic Timing of AntiRetroviral Treatment (START) 2015



Recommendations for Initiation of Antiretroviral Therapy in Adults

EACS 2017: ART is recommended in all adults with chronic HIV infection, irrespective of CD4 counts http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

WHO 2016: ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count

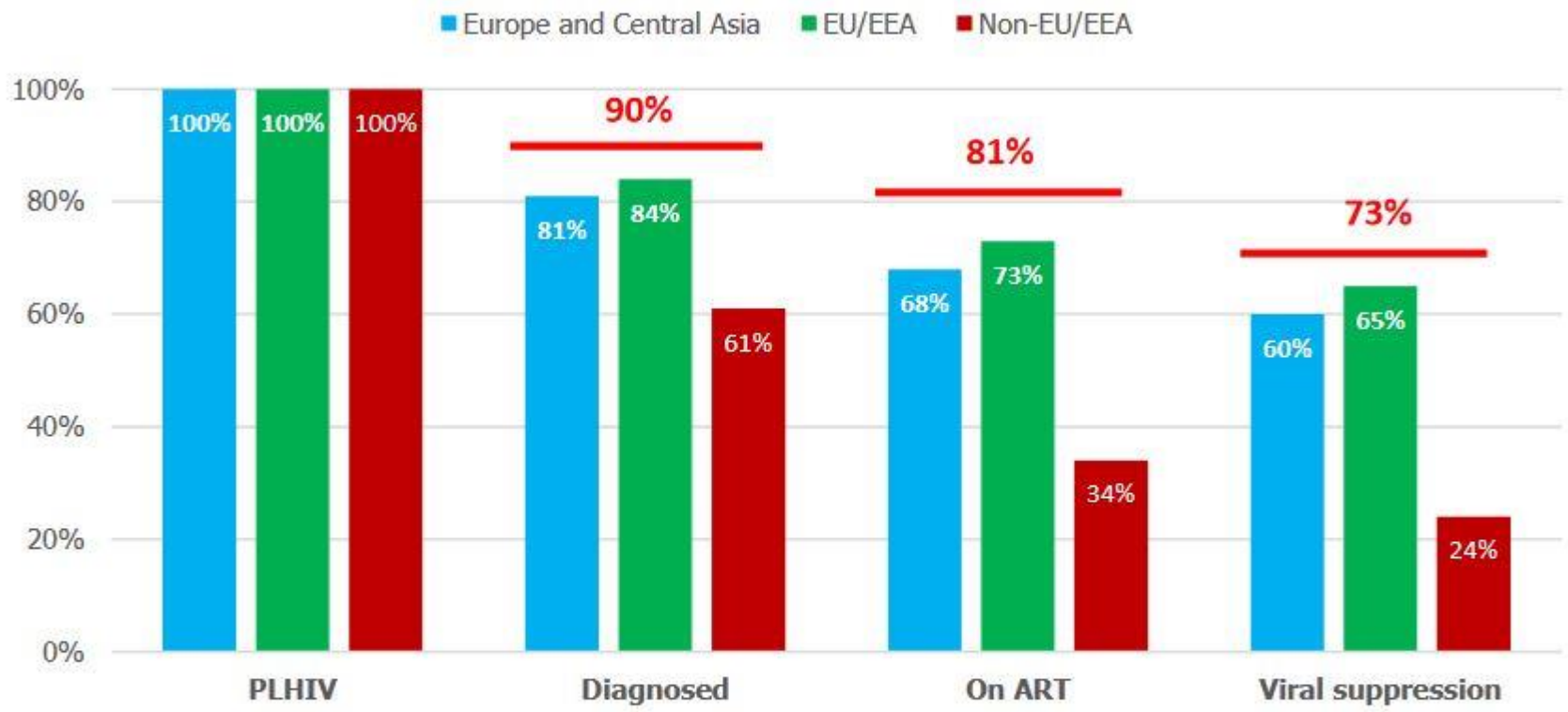
http://www.who.int/hiv/pub/arv/arv-2016/en/

Does ART Reach Everybody?

Continuum of care: HIV Treatment Cascade (Diagnosis → Treatment → Undetectable Viral Load)

# of late presenters (<350 CD4/mm^3 or AIDS-defining disease regardless of CD4; European Consensus 2011)

Figure 8. Viral suppression among all PLHIV in the 29 countries with data on all four stages of the continuum of care, EU/EEA and non-EU/EEA countries, 2016[28]

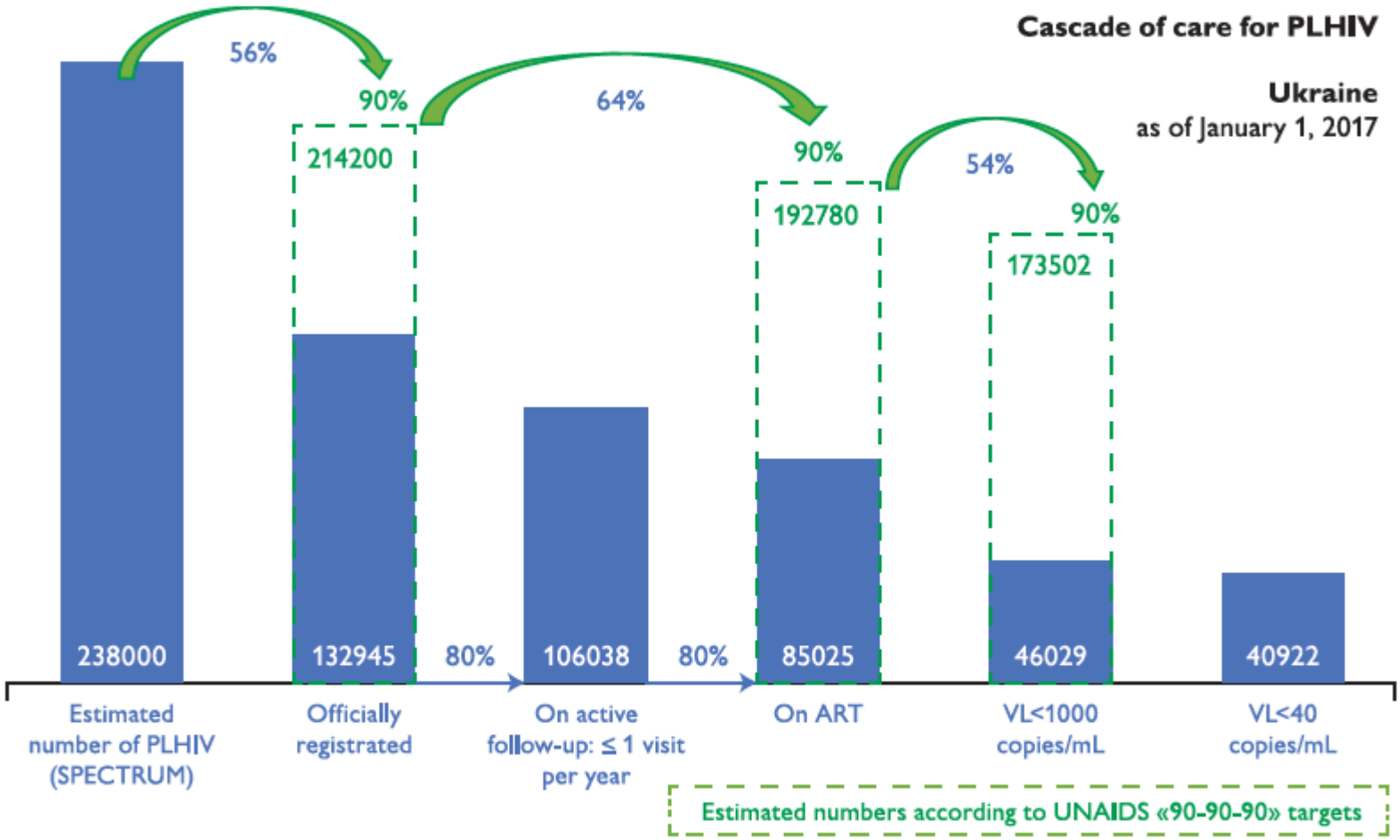


No data from:

EU/EEA countries: Cyprus, Czech Republic, Estonia, Finland, Iceland, Ireland, Latvia, Liechtenstein, Lithuania, Norway, Poland, Slovakia, Slovenia.
Non-EU/EEA countries: Andorra, Belarus, Bosnia and Herzegovina, the Former Yugoslav Republic of Macedonia, Israel, Kosovo*, Monaco, Russia, San Marino, Turkey, Turkmenistan, Ukraine, Uzbekistan.

Source: European Centre for Disease Prevention and Control (ECDC)

Figure 1. **The cascade of services for people living with HIV in Ukraine (as of January 2017)**[7]



6 OST program data. Retrieved on April 7, 2017 from: http://phc.org.ua/pages/diseases/opioid_addiction/stat-docs

7 National Public Health Center of the Ministry of Health of Ukraine & USAID RESPOND Project.

Do all populations / groups of PLWHIV benefit?

- frequent lack of data
- tailored HIV care programs
- integration of services (e.g., STI screening, TB care)

Risher et al. HIV treatment cascade in MSM, people who inject drugs, and sex workers. Curr Opin HIV AIDS 2015, 10:420–429 DOI:10.1097/COH.0000000000000200

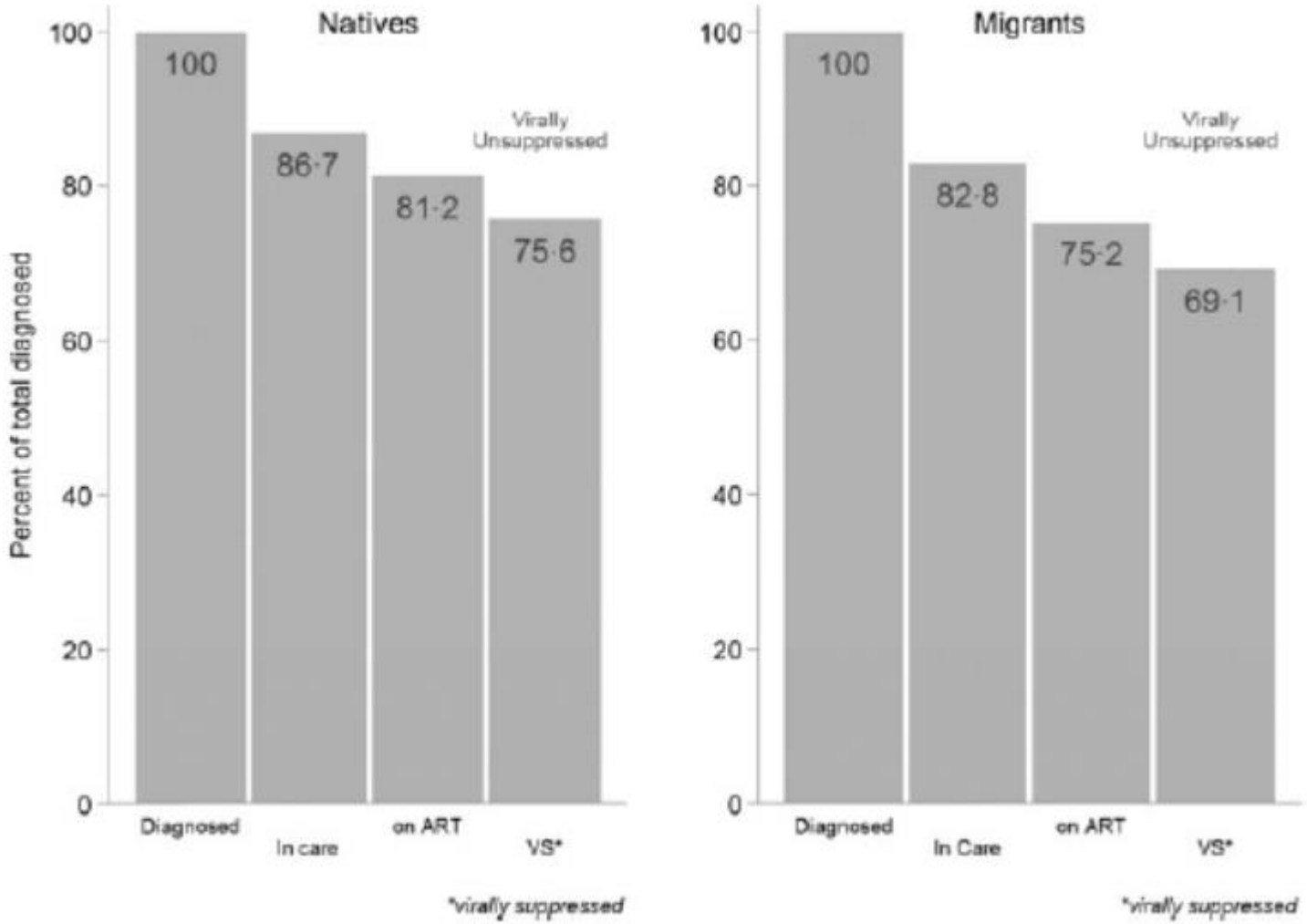
Cohort of the Spanish AIDS Research Network (CoRIS)

- Compared with NSP, SSA and LAC under 35 years of age had a higher risk of delayed diagnosis

- no major differences in time to ART requirement or initiation

- poorer virological and immunological response was observed in SSA (viral subtype? Mutations?)

Monge et al. Inequalities in HIV disease management and progression in migrants from Latin America and sub-Saharan Africa living in Spain. HIV Med. 2013 May;14(5):273-83. doi: 10.1111/hiv.12001



HIV healthcare cascade comparing the Spanish-born population with migrants, Catalonia – Sp

Reyes-Urueña Epidemiol. Infect. 2017 doi:10.1017/S0950268817000

Late presenters Switzerland

- 1366 patients enrolled in the Swiss HIV Cohort Study (SHCS) 2009-2012
- late presentation occurred in 49.8%
- more frequent among women and individuals from sub-Saharan Africa

Hachfeld et al. J Int AIDS Soc. 2015;18:20317. doi: 10.7448/IAS.18.1.20317

Demographic characteristics of late and non-late presenters

	Late presenters	Non-late presenters	
	N=680 (49.8%)	*N*=686 (50.2%)	*p*
Demographic group (%)			<0.001
MSM	278 (40.9)	421 (61.4)	
Non-MSM male	198 (29.1)	128 (18.6)	
Female	204 (30.0)	137 (20.0)	
Median age in years (IQR)	40.6 (32.7–48.4)	38.2 (31.0–45.4)	<0.001
Median first CD4 count in cells/µl (IQR)	195 (88–286)	511 (417–663)	<0.001
Region of origin (%)			<0.001
South + Northwest Europe	435 (64.0%)	515 (75.3%)	
Sub-Saharan Africa	126 (18.6%)	69 (10.1%)	
South + East Asia	51 (7.5%)	17 (2.5%)	
Other	67 (9.9%)	83 (12.1%)	
High-level education (%)	242 (35.6%)	297 (43.4%)	0.002

IQR, interquartile range; MSM, men who have sex with men.

Hachfeld et al.

SHCS

Main patient-related reasons for late testing:

- not feeling at risk (72%)
- not feeling ill (65%)
- not knowing the symptoms of HIV (51%)

Hachfeld et al.

Netherlands

ATHENA Cohort 1/1996-6/2014:

- Of 20,965 patients, 53% presented with late-stage HIV infection, and 35% had advanced disease

- heterosexual males, migrant populations, people aged ≥50 years

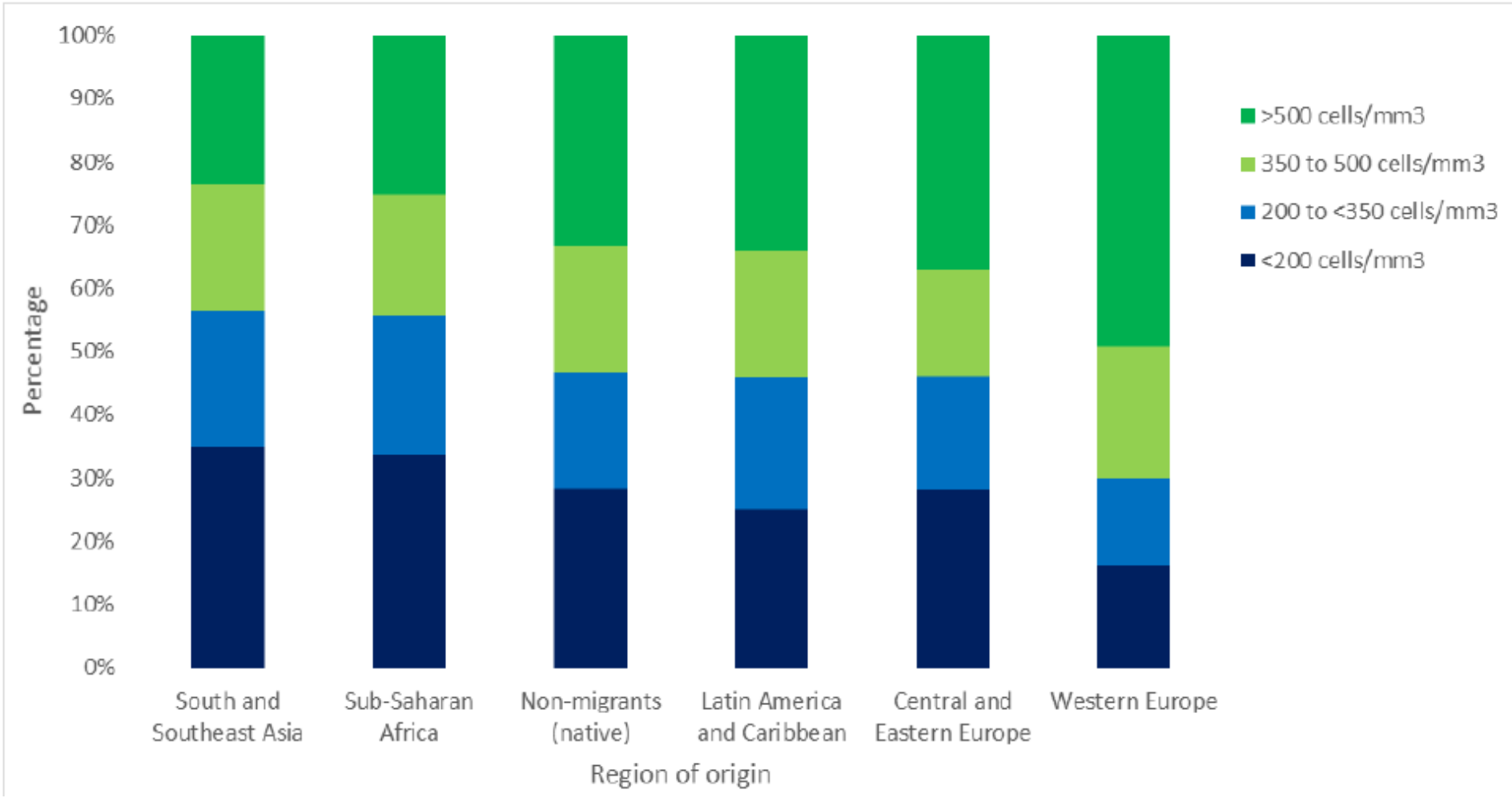
Op de Coul EL et al; ATHENA National Observational HIV Cohort. Factors associated with presenting late or with advanced HIV disease in the Netherlands, 1996-2014: results from a national observational cohort. BMJ Open. 2016 Jan4;6(1):e009688. doi: 10.1136/bmjopen-2015-009688et al.

Characteristics of HIV patients with non-late presentation, late presentation and advanced disease in the Netherlands, January 1996 to June 2014

	HIV patients in care, total (n=20 965, 100%) N (%)	'Timely' presentation (n=5756, 27%) N (%)	Late presentation (n=11 182, 53%) N (%)	Advanced disease (n=7331, 35%) N (%)
Region of origin				
The Netherlands	11 913 (57)	3643 (63)	5866 (52)	3808 (52)
Europe, else	2006 (10)	626 (11)	962 (9)	627 (9)
SSA	3201 (15)	544 (9)	2156 (19)	1424 (19)
Surinam	928 (4)	215 (4)	568 (5)	377 (5)
Netherlands Antilles/Caribbean	821 (4)	221 (4)	443 (4)	291 (4)
Latin America	621 (3)	172 (3)	306 (3)	192 (3)
South-East Asia	712 (3)	132 (2)	470 (4)	337 (5)
Else/unknown	763 (4)	203 (4)	411 (4)	275 (4)

Op de Coul EL et al

Figure 3. Late diagnosis of HIV among migrants in the EU/EEA, 2015



ECDC Special Report HIV and Migrants 2017

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Table 6. Countries reporting factors contributing to late diagnosis among migrants (n=48), 2016

	Migrants from high-prevalence countries	Undocumented migrants
Low risk perception	19 (40%)	15 (31%)
Fear of knowing one's HIV status	17 (35%)	14 (29%)
Lack of knowledge about HIV	16 (33%)	12 (25%)
Denial of risk behaviours	13 (27%)	9 (19%)
Limited screening of people with HIV risk factors when they are still asymptomatic	13 (27%)	11 (23%)
Inadequate efforts by health professionals to offer HIV testing to people at risk of infection	10 (21%)	10 (21%)

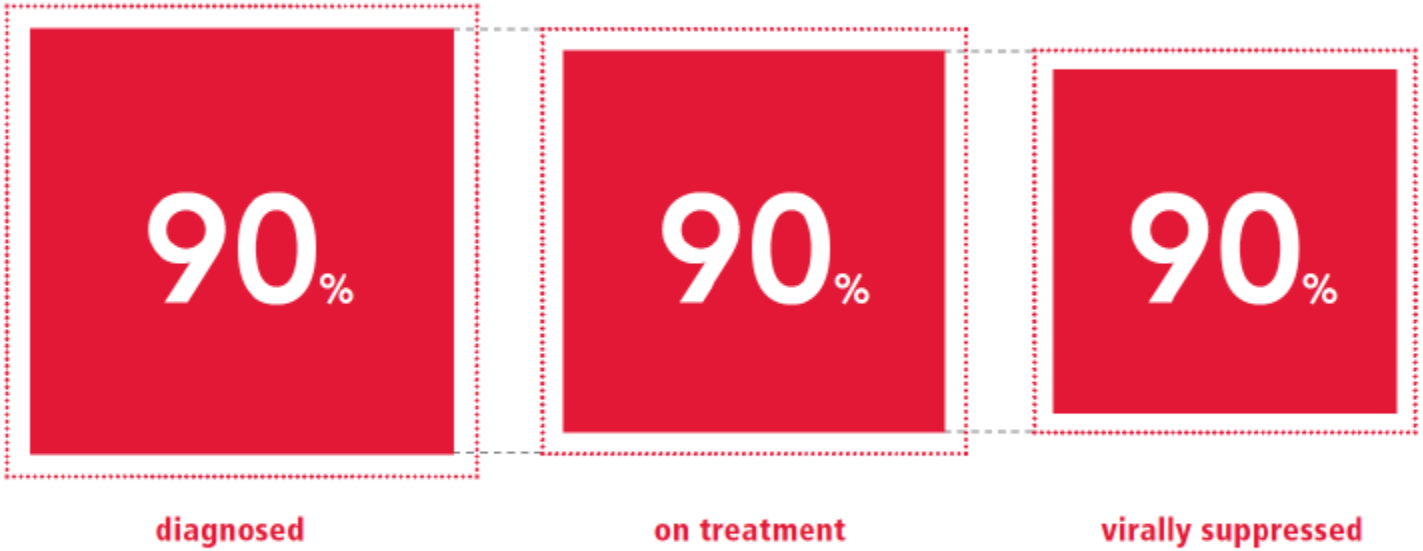
ECDC Special Report HIV and Migrants 2017

TasP:

Treatment as (Primary) Prevention

- The use of antiretroviral therapy to reduce the risk of HIV transmission

An Ambitious Treatment Target to END* the AIDS Pandemic



THE FINAL CHAPTER OF THE AIDS EPIDEMIC

90-90-90 = 90-81-73

** Defined as decreasing overall disease burden (M&M&T) by 90% from global 2010 levels*

http://www.unaids.org/en/resources/documents/2017/90-90-90

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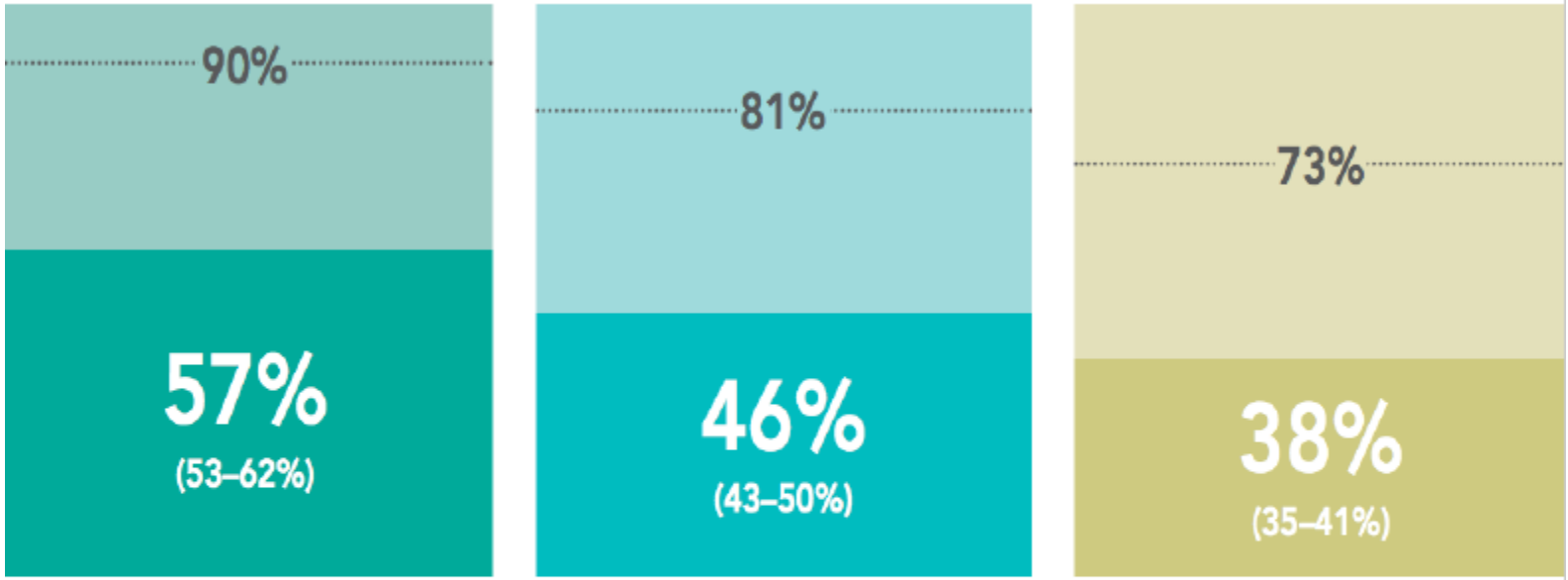
UN 90-90-90 Target: Global Status in 2015



ercentage of people living with
IV who know their HIV status[1]

Percentage of people living with HIV who are on antiretroviral treatment

Percentage of people living with HIV who are virally suppressed[2]

2015 measure derived from data reported by 87 countries, which accounted for 73% of people living with HIV worldwide.
2015 measure derived from data reported by 86 countries. Worldwide, 22% of all people on antiretroviral therapy were reported to have received a viral load test during the reporting period.

HEALTH GAP, UN 90-90-90 Workshop, Durban, July 2016

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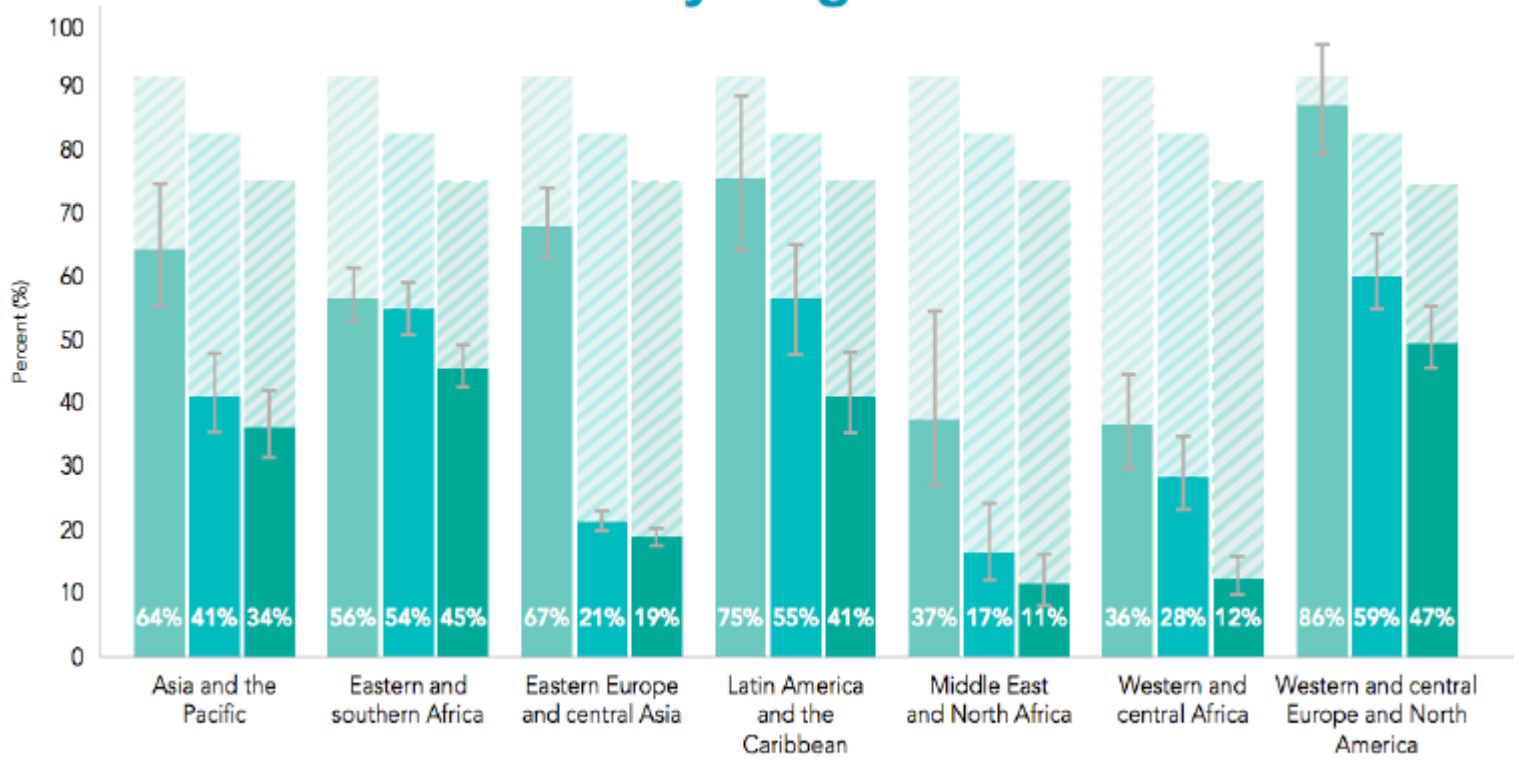
UN 90-90-90 Target: Global Status in 2015
By Region



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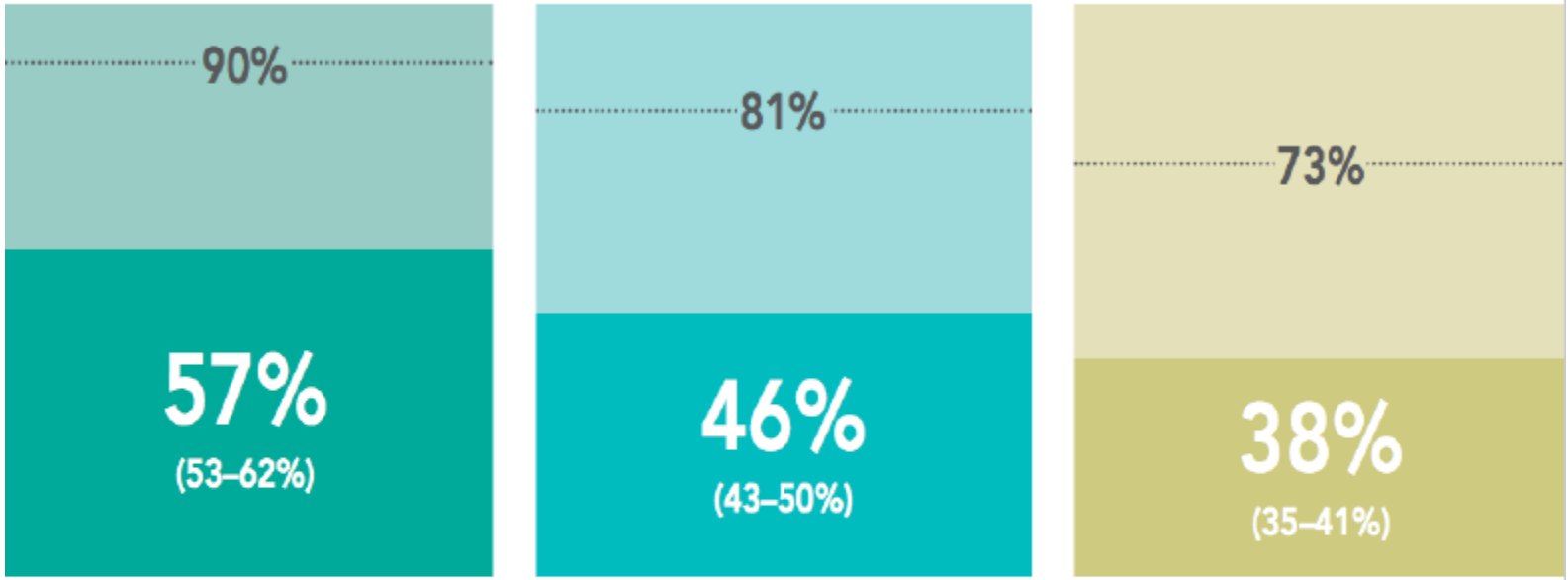

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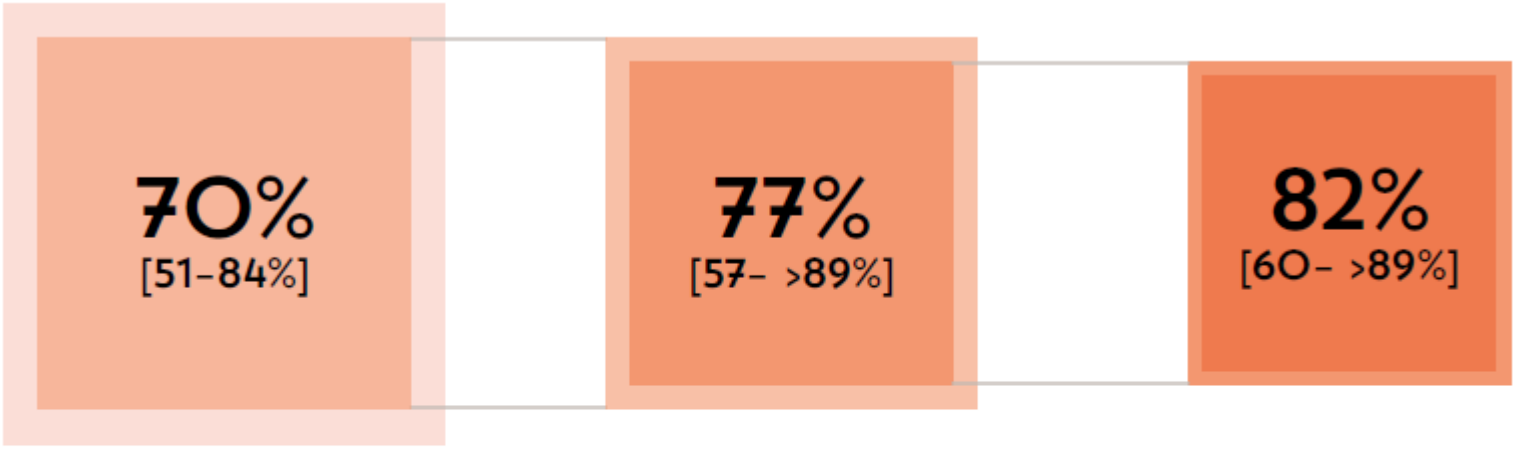

FIGURE 3.1. PROGRESS TOWARDS THE 90–90–90 TARGETS, GLOBAL, 2016

Source: UNAIDS special analysis, 2017; see annex on methods for more details.

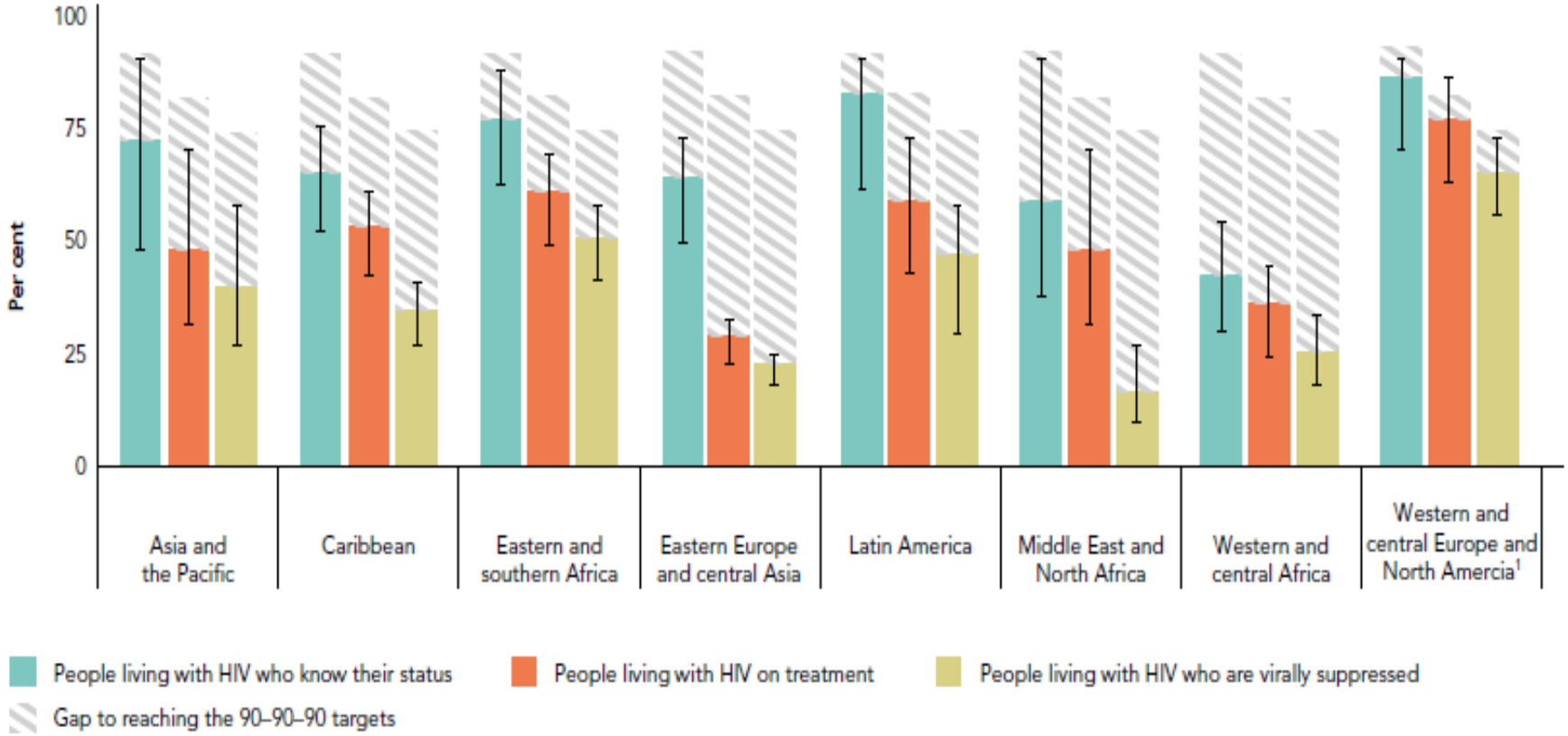

FIGURE 3.3. KNOWLEDGE OF HIV STATUS, TREATMENT COVERAGE AND VIRAL LOAD SUPPRESSION, BY REGION, 2016