



Benefits of Antiretroviral Therapy

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Sitges 23 March 2018





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)



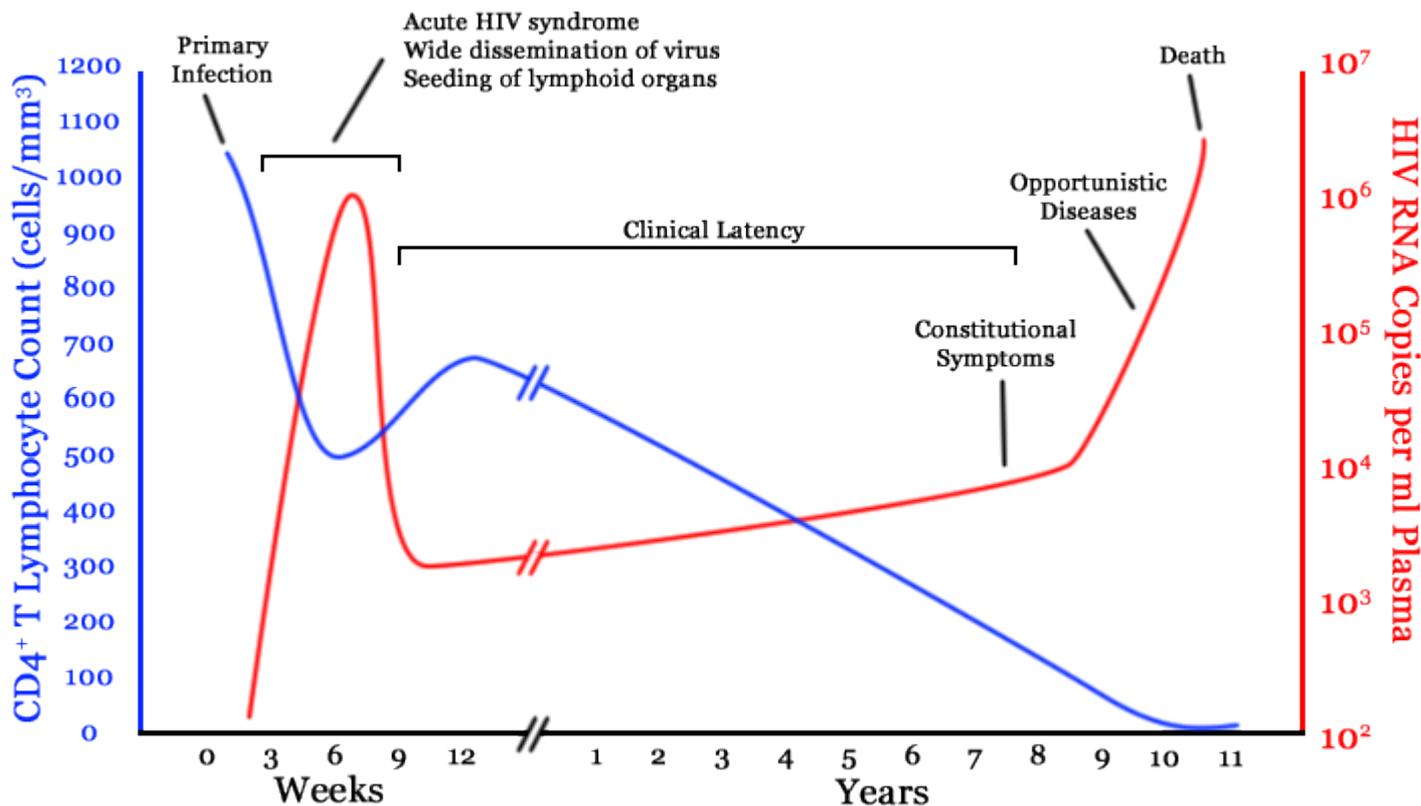


HIV: incubation period (= latency period, asymptomatic phase) from HIV infection to AIDS ~10 years

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>

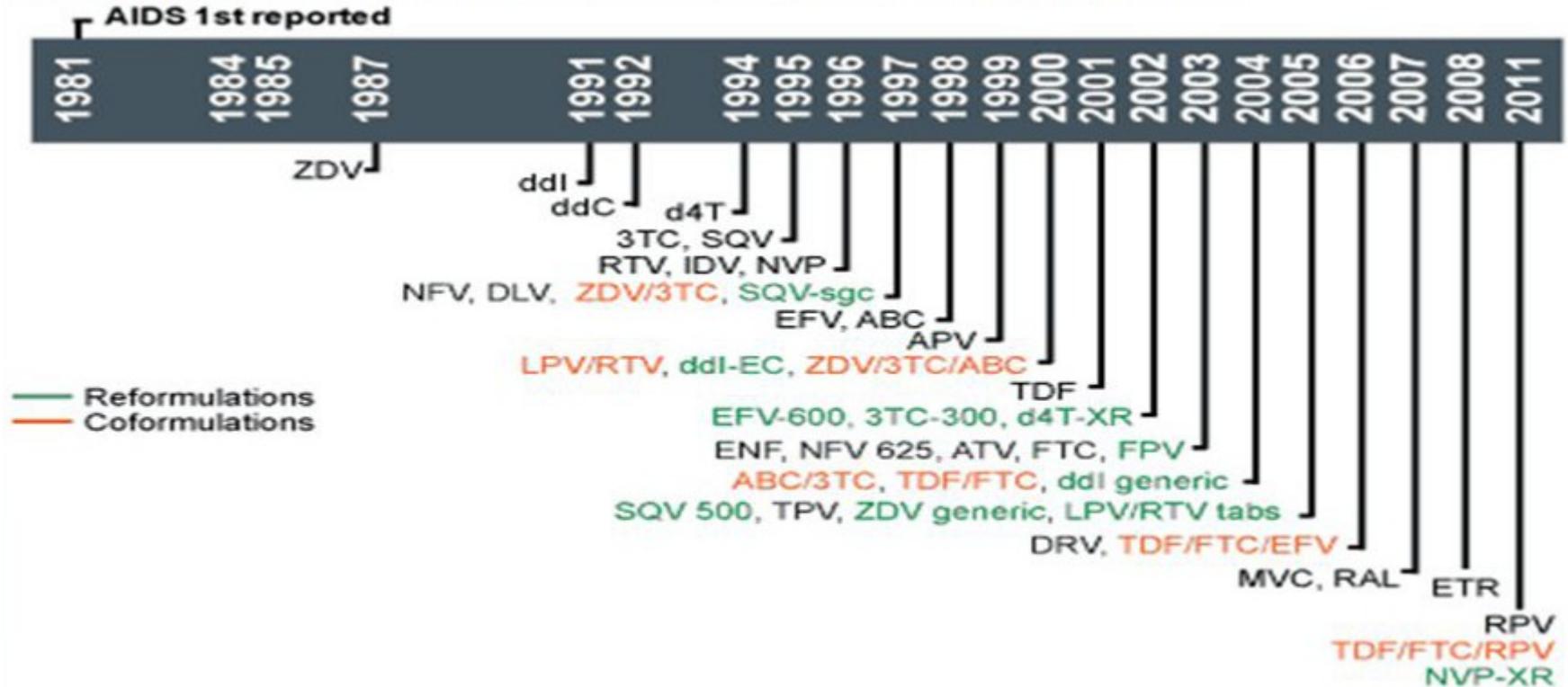




Fauci Ann Intern Med. 1996;124(7):654-663

<http://annals.org/aim/fullarticle/709558/immunopathogenic-mechanisms-hiv-infection>

Figure 1. Timeline for development of antiretroviral agents.



3TC, lamivudine; ABC, abacavir; APV, amprenavir; ATV, atazanavir; d4T, stavudine; ddC, zalcitabine; ddl, 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.

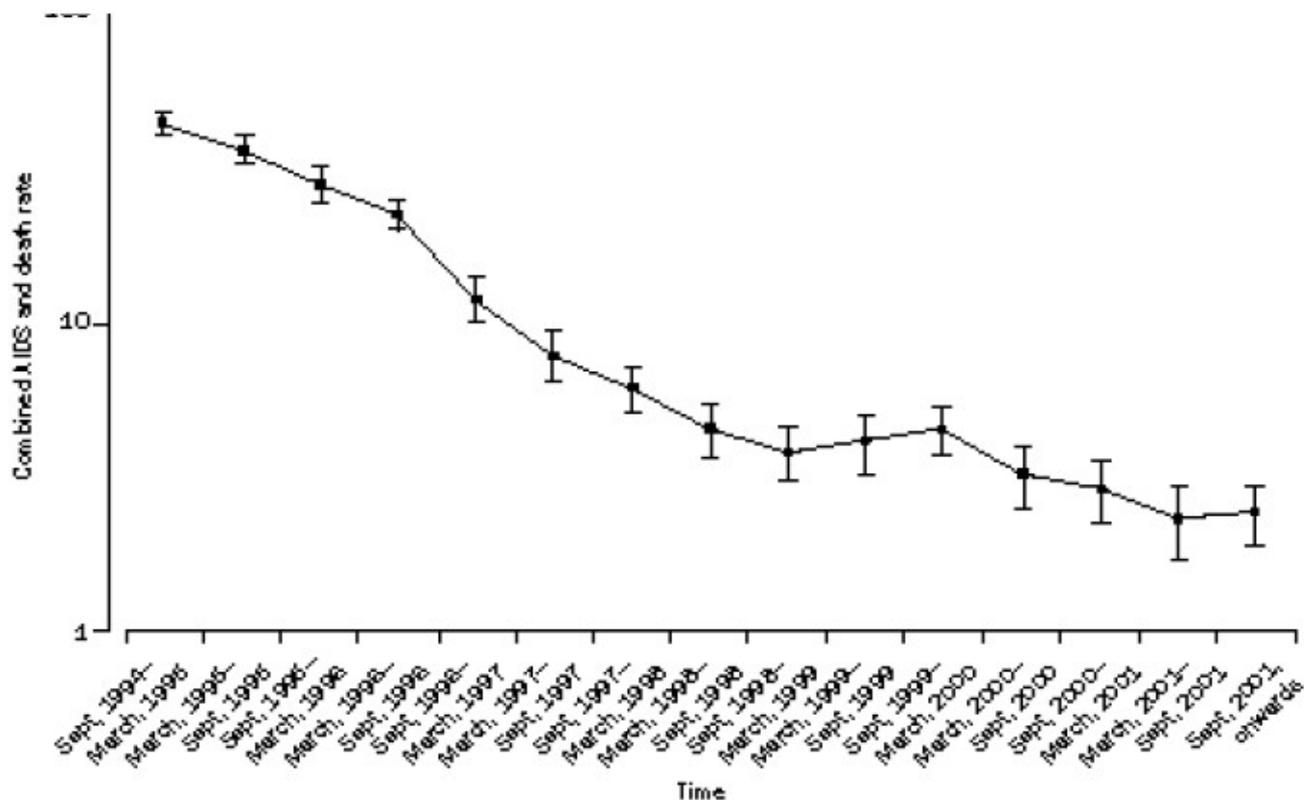


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1996ff HAART / cART

Decline of

- AIDS-defining disorders (esp. opportunistic infections and tumors)
- mortality due to AIDS
- overall mortality



Events (n)	522	351	227	292	146	87	140	105	84	88	114	80	69	58	73
Median CD4 (cells/ μ L) at event (IQR)	29 (10-84)	27 (3-100)	30 (10-100)	31 (10-87)	62 (15-161)	89 (33-223)	108 (47-208)	127 (45-244)	149 (40-265)	100 (26-222)	125 (40-266)	150 (30-313)	187 (80-303)	220 (107-403)	220 (80-397)

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



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
- occurrence of AIDS before initiation of cART resulted in poorer prognosis
- argument in favor of an earlier initiation of antiretroviral therapy



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
- CD4 counts were all over 500 cells/mm³
- study participants were randomised to start ART immediately or have deferred treatment until their CD4 cell count declined to 350 cells/mm³



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

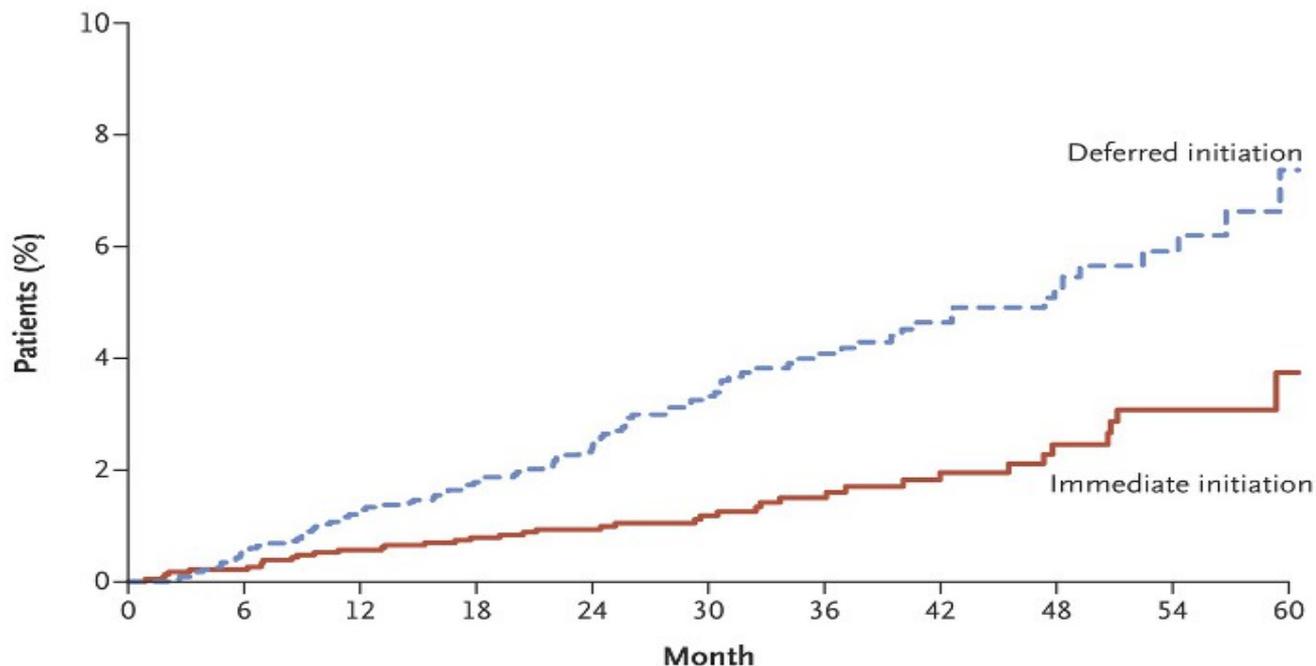
<http://www.aidsmap.com/START-trial-finds-that-early-treatment-improves-outcom>

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



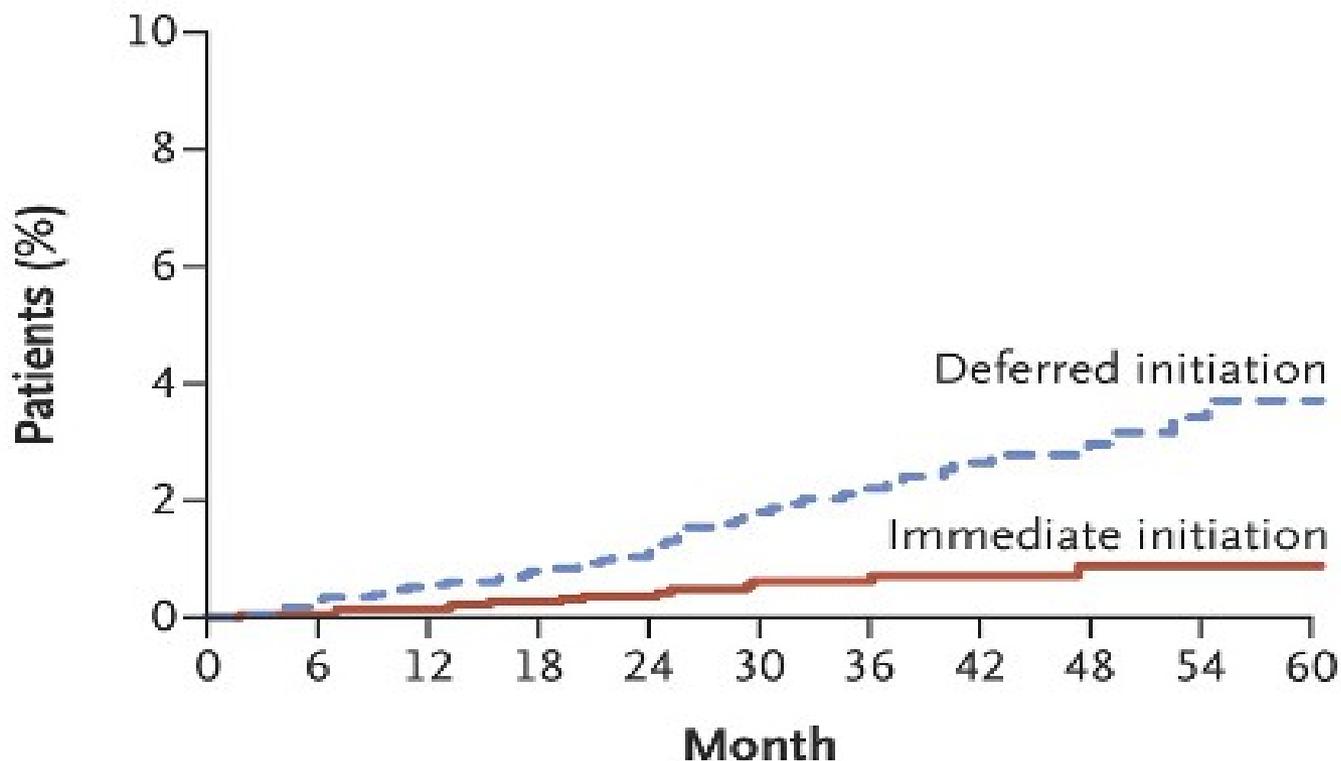
Strategic Timing of AntiRetroviral Treatment (START) 2015

A Time to First Primary Event



Strategic Timing of AntiRetroviral Treatment (START) 2015

B Serious AIDS-Related Event





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/>





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Does ART Reach Everybody?

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

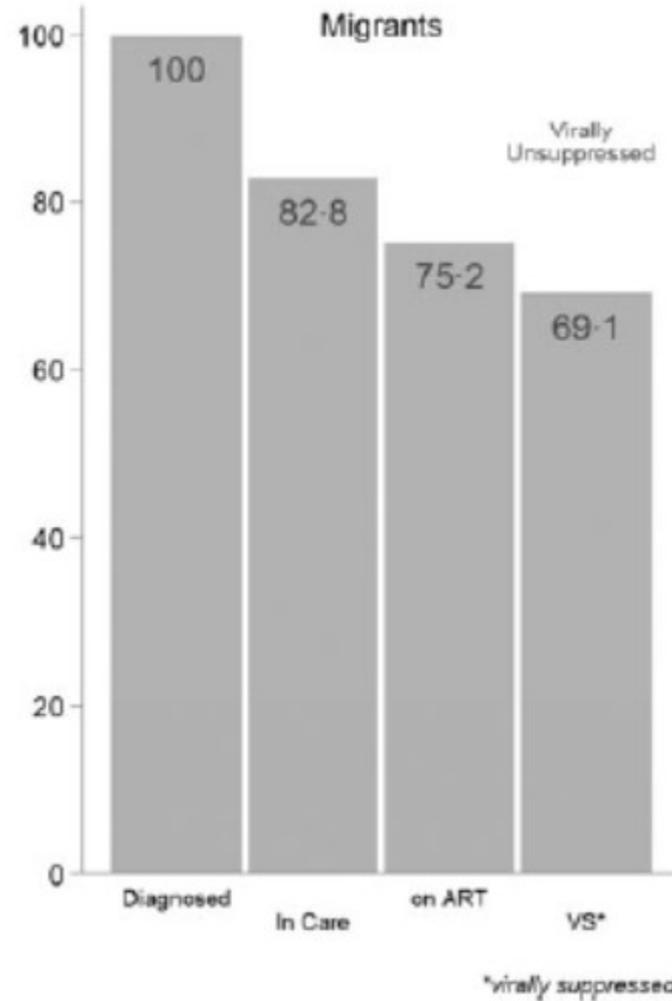
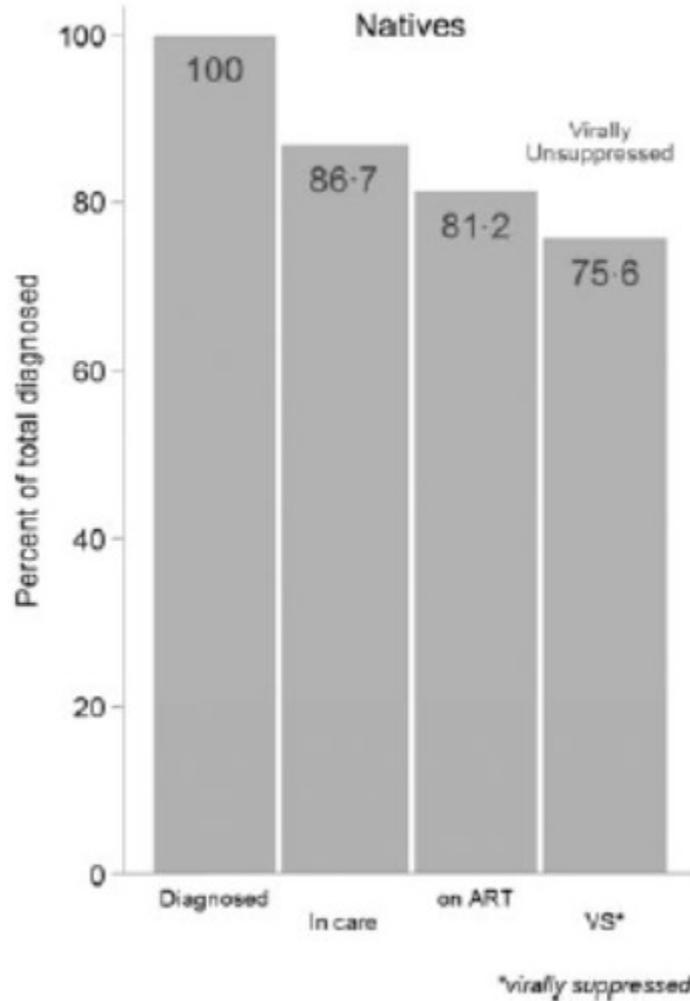
of late presenters (<350 CD4/mm³ or AIDS-defining disease regardless of CD4; European Consensus 2011)



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



Swiss HIV Cohort Study (SHCS)

- immigrants underrepresented
- people from SSA having greatest probability of nonparticipation
- patients from SE Asia enrolled with most advanced disease stage
- higher loss to follow-up for immigrants

Thierfelder HIV Med. 2012 Feb;13(2):118-26

Doi: 10.1111/j.1468-1293.2011.00949.x





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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	<i>p</i>
	N=680 (49.8%)	N=686 (50.2%)	
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	821 (4)	221 (4)	443 (4)	291 (4)
Antilles/Caribbean				
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)

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

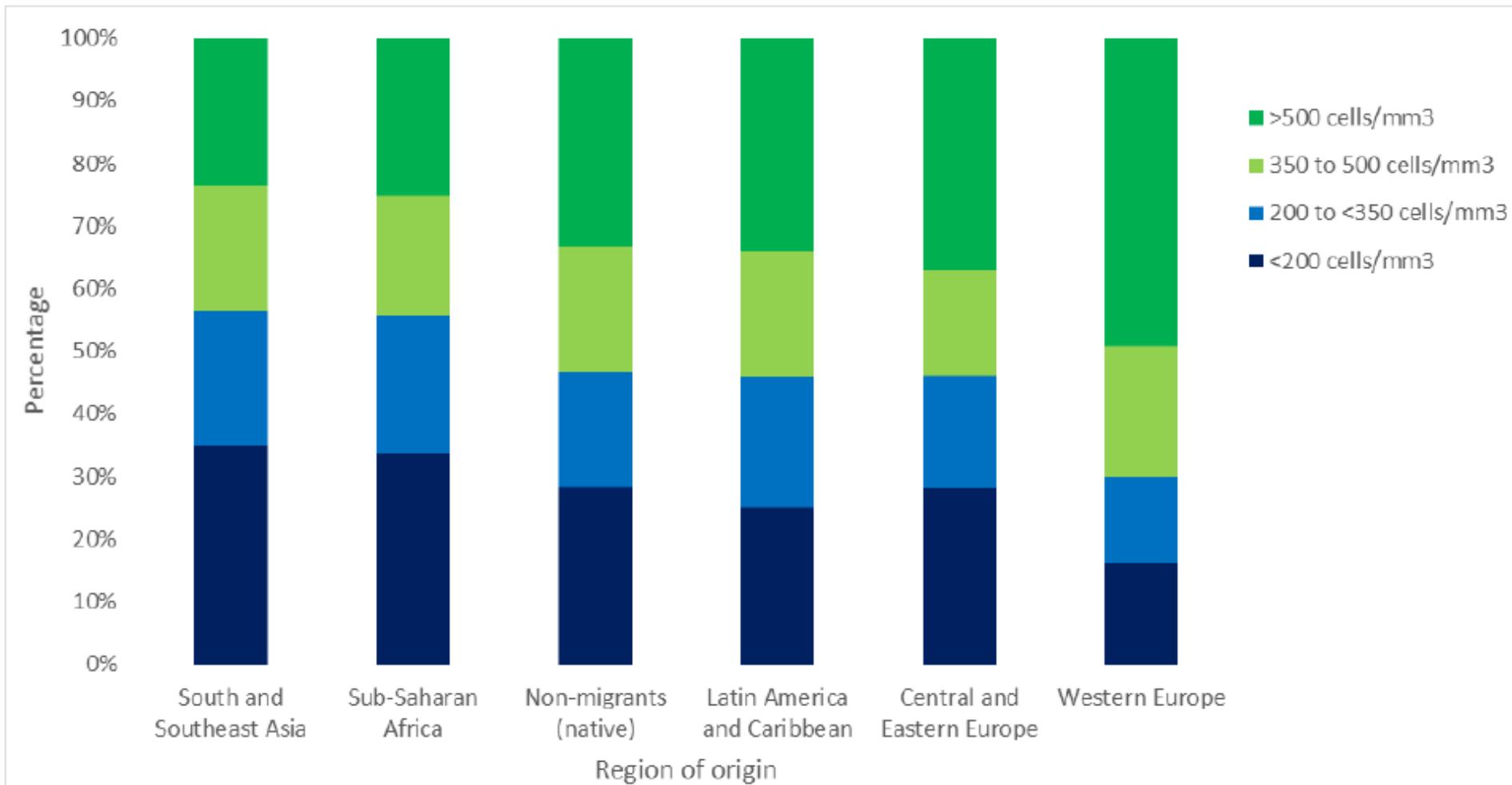


Table 6. Countries reporting factors contributing to late diagnosis among migrants (n=48), 2016

	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%)



Germany

- 2001-2010 49.5% late presenters (11,352 of 22,925)
- ~17% were migrants
- 'There is clearly a need to identify and lower individual, cultural, and language- and community-related, as well as structural barriers to disease-related knowledge, awareness, and diagnosis in migrant populations in Germany.'

Zoufaly A et al. Late presentation for HIV diagnosis and care in Germany. HIV Med. 2012 Mar;13(3):172-81. doi:10.1111/j.1468-1293.2011.00958.x



TasP:

Treatment as (Primary) Prevention

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





'Swiss Statement' (1/2)

“An HIV-infected person on antiretroviral therapy with completely suppressed viraemia (“effective ART”) is not sexually infectious, i.e. cannot transmit HIV through sexual contact.”

Vernazza et al. HIV-infizierte Menschen ohne andere STD sind unter wirksamer antiretroviraler Therapie sexuell nicht infektiös. Bull Med Suisses 2008;89:165–69

<https://saez.ch/de/article/doi/saez.2008.13252/>



'Swiss Statement' (2/2)

as long as:

- the person adheres to antiretroviral therapy, the effects of which must be evaluated regularly by the treating physician, and
- the viral load has been suppressed (< 40 copies/ml) for at least six months, and
- there are no other sexually transmitted infections

Vernazza et al. HIV-infizierte Menschen ohne andere STD sind unter wirksamer antiretroviraler Therapie sexuell nicht infektiös. Bull Med Suisses 2008;89:165–69

<https://saez.ch/de/article/doi/saez.2008.13252/>



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HIV Prevention Trials Network (HPTN 052) study

- the use of ARVs by HIV-positive heterosexual men and women cuts the chance that their HIV-negative partner becomes infected
- no participant with a fully suppressed viral load transmitted the virus to his or her long-term HIV-negative partner

Cohen et al. N Engl J Med 2016; 375:830-839
<http://www.nejm.org/doi/full/10.1056/NEJMoa1600693>





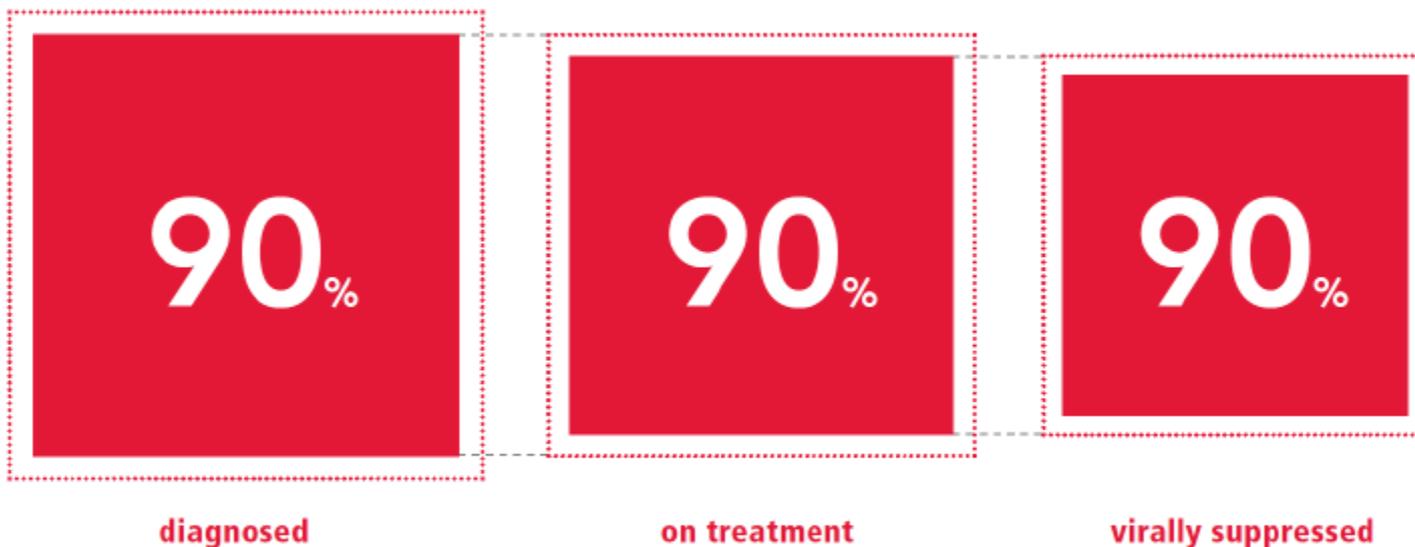
PARTNER trial

- heterosexual and gay mixed (serodiscordant) HIV-status couples in which the HIV-positive partner is taking ART
- zero HIV transmissions from over 58,000 individual times that people had sex without condoms when the partner with HIV remained undetectable (i.e., had a fully suppressed virus)

Rodger AJ et al. JAMA, 2016;316(2):1-11. DOI: 10.1001/jama.2016.5148.
<http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2016.5148>



An Ambitious Treatment Target to END* the AIDS Pandemic



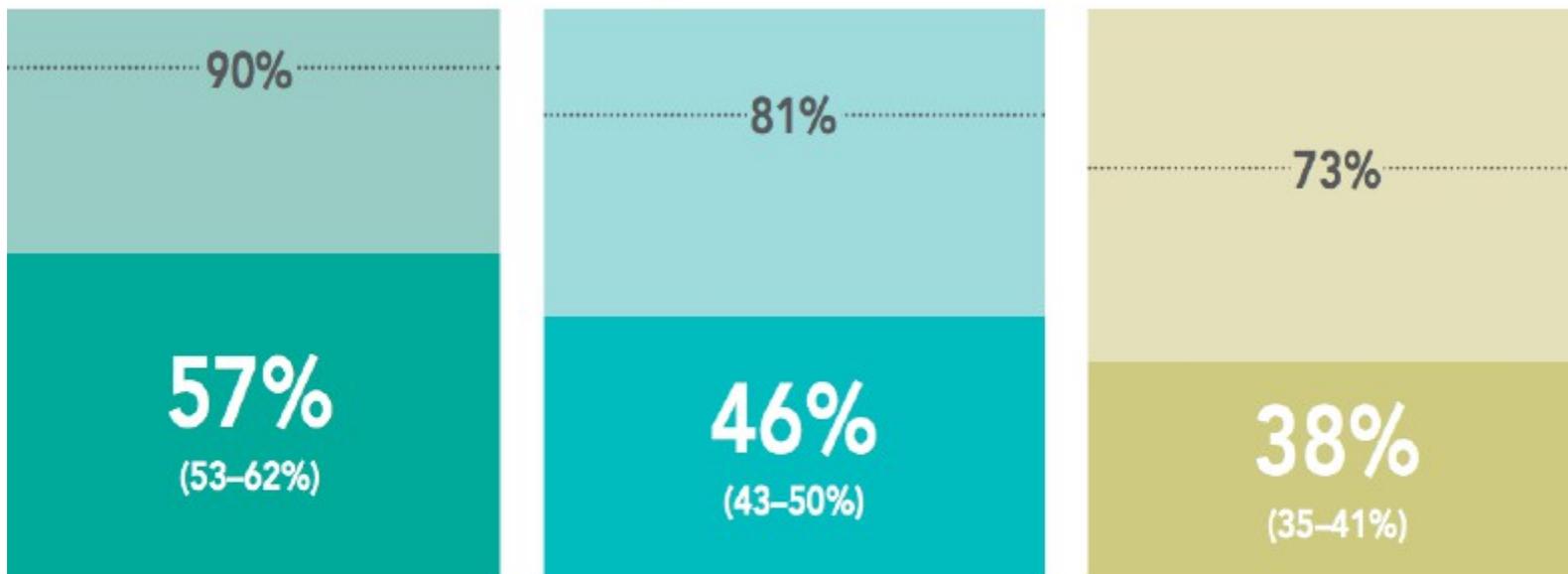
THE FINAL CHAPTER OF THE AIDS EPIDEMIC

90-90-90 = 90-81-73

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



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



Percentage of people living with HIV who know their HIV status¹

Percentage of people living with HIV who are on antiretroviral treatment

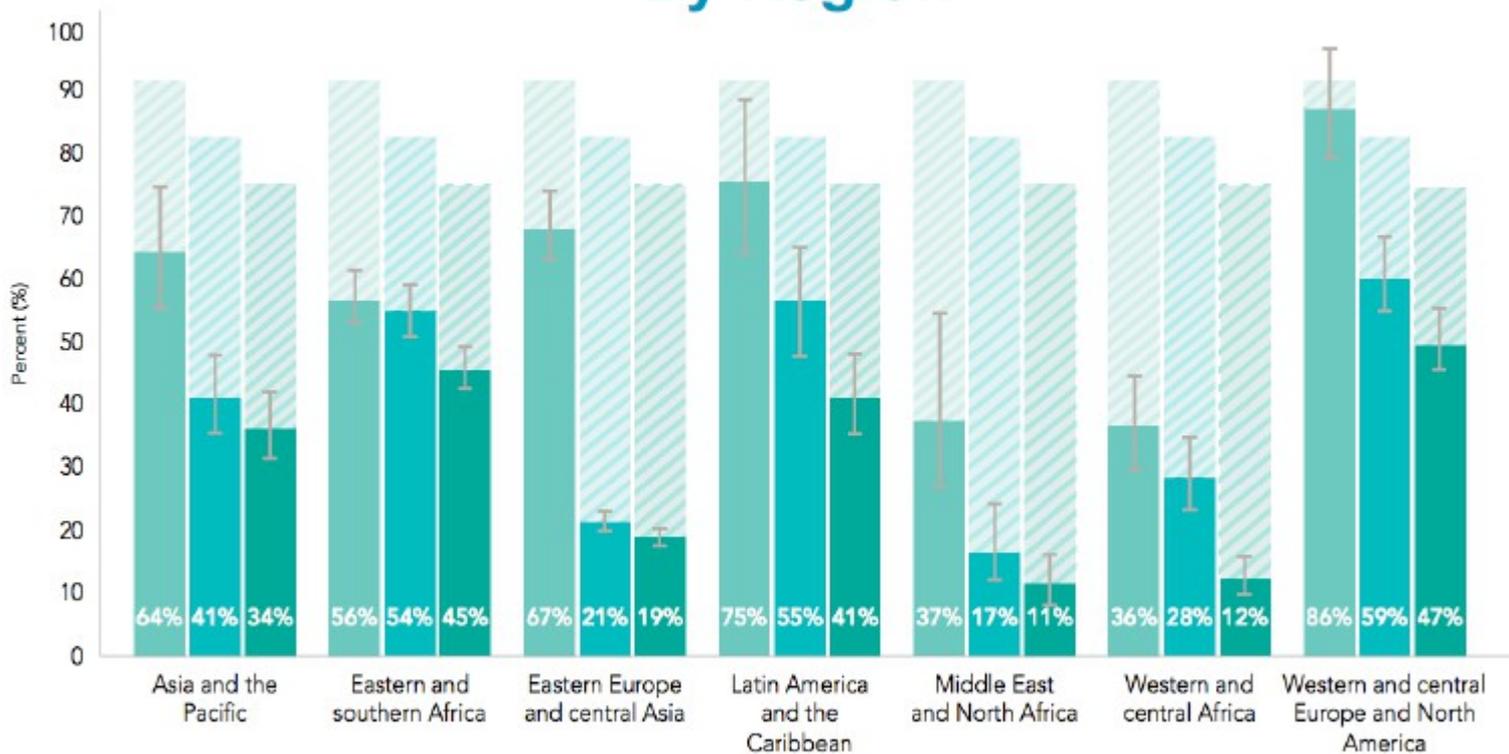
Percentage of people living with HIV who are virally suppressed²

¹2015 measure derived from data reported by 87 countries, which accounted for 73% of people living with HIV worldwide.

²2015 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

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



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