When Early Is Not Early Enough:
Late Presentation and Same Day ART Initiation

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FINANCIAL DISCLOSURES

- Consultant:
  - Gilead Sciences, Merck & Co., ViiV Healthcare
- Research Support (to Apex Research):
  - Gilead Sciences, Merck & Co., ViiV Healthcare

OVERVIEW

- HIV care continuum and late diagnosis in Europe
- Optimizing the care continuum
- When to start ART
- Same-day ART?

HIV CARE CONTINUUM IN EUROPE

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UNAIDS 90-90-90 TARGETS

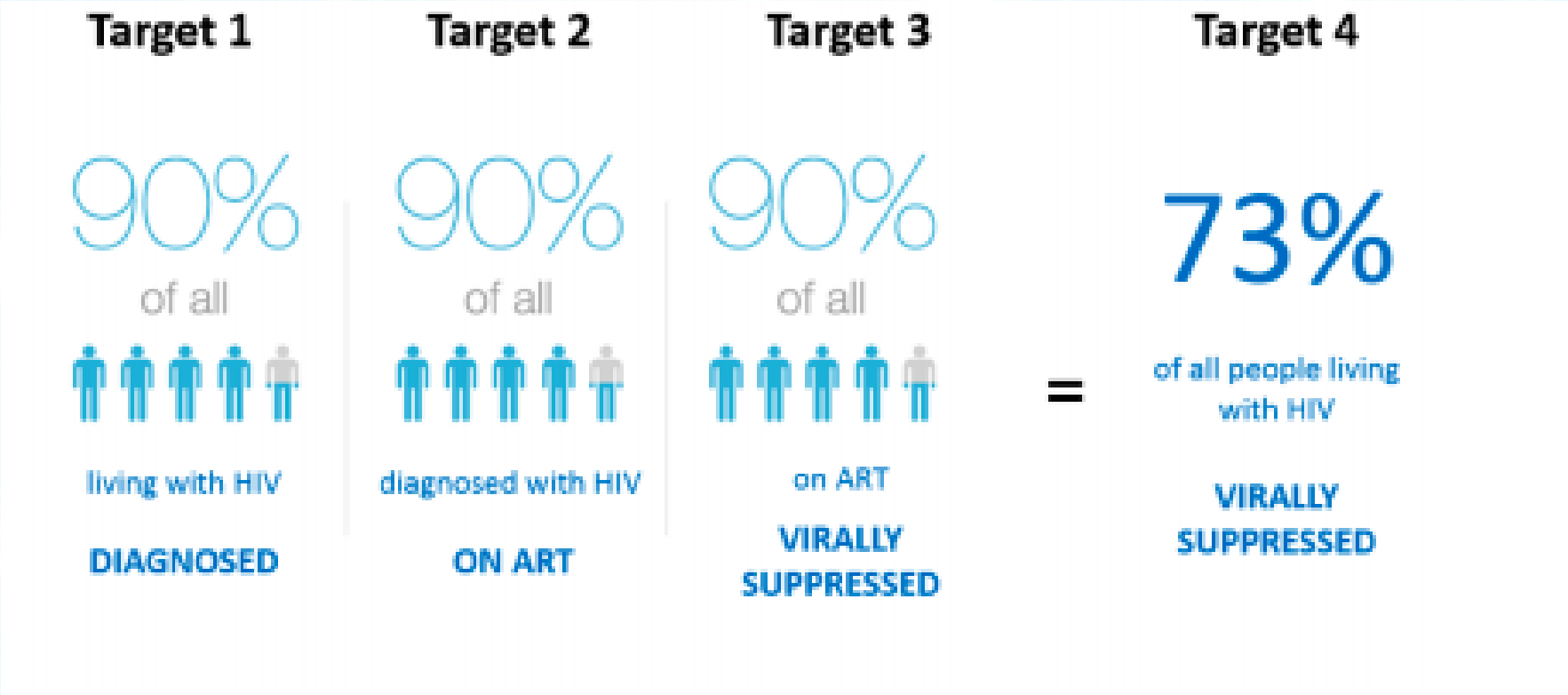

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Figure 4. Percentage of all PLHIV who know their status in 37 countries of Europe and Central Asia, 2016[20]

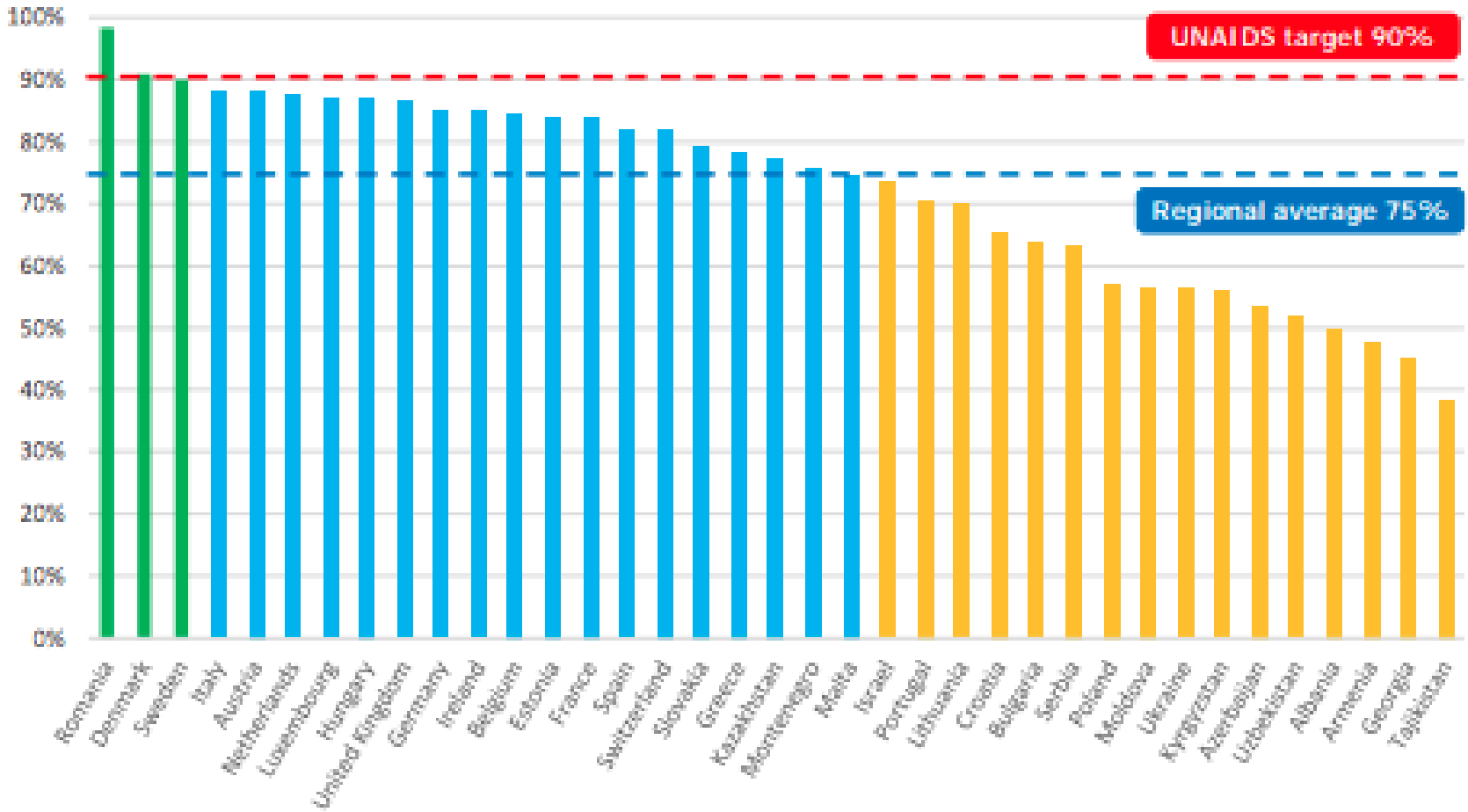


Figure 5. Proportion of people diagnosed with HIV receiving ART in Europe and Central Asia, 2016[22]

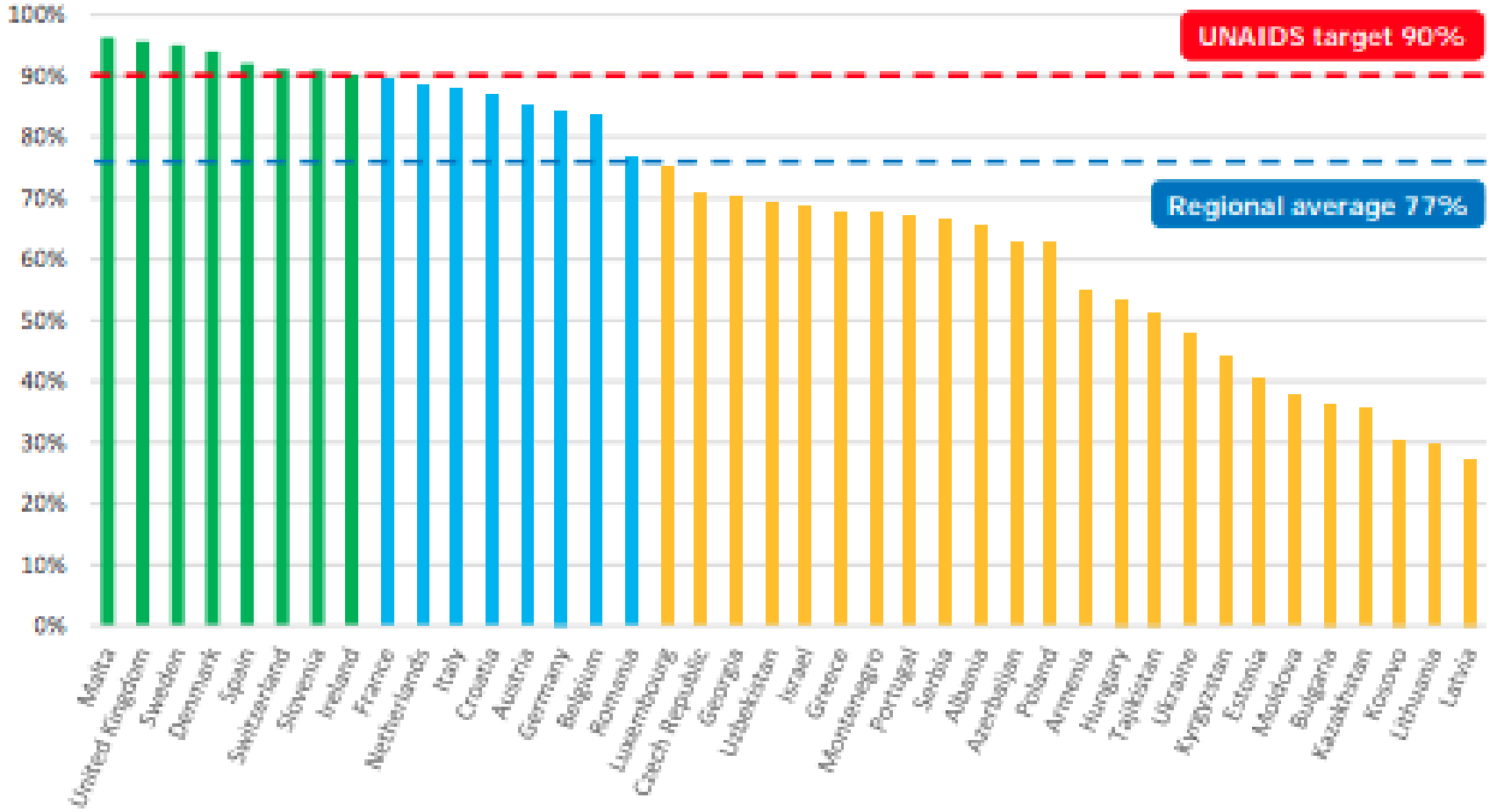
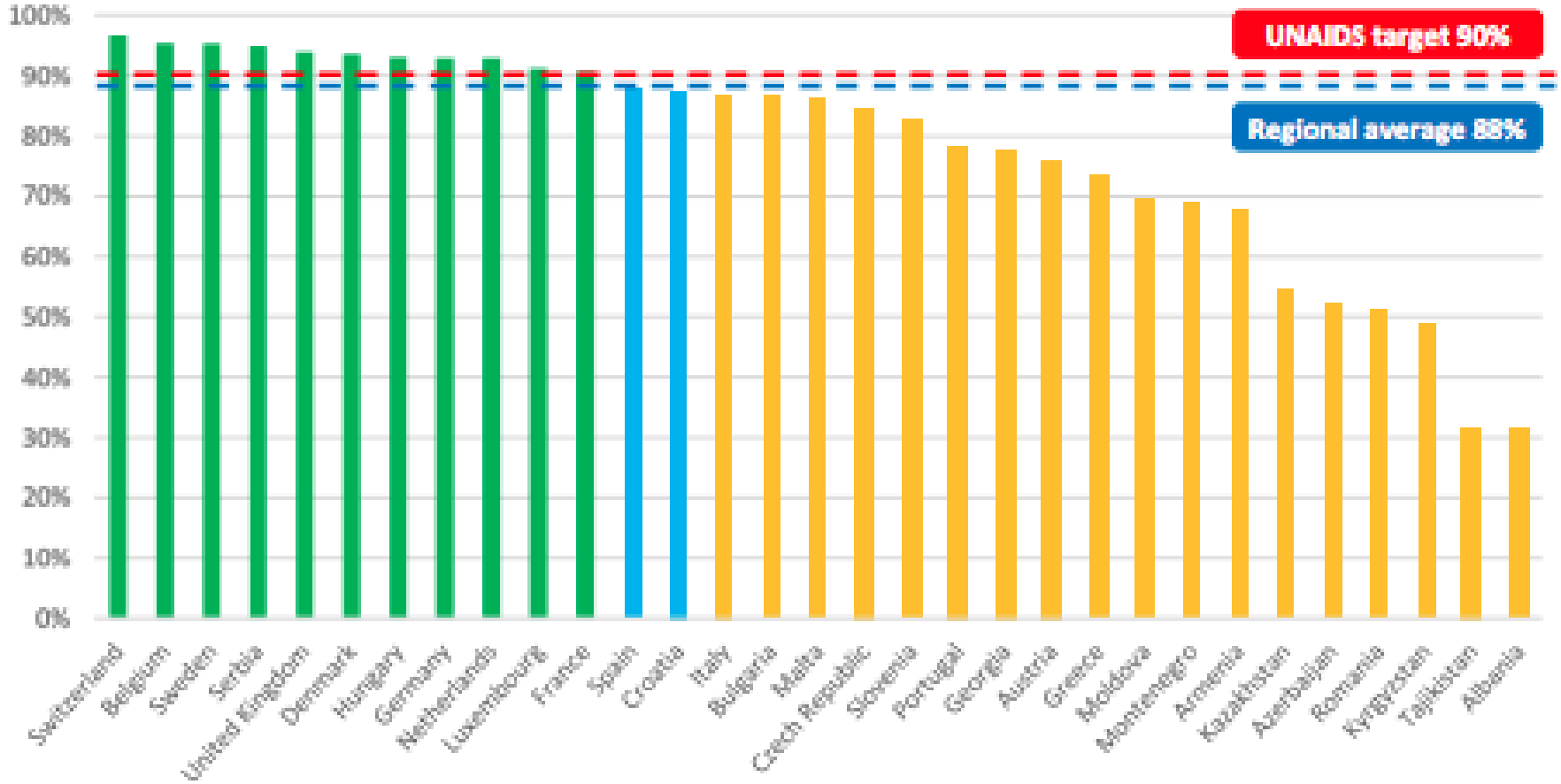
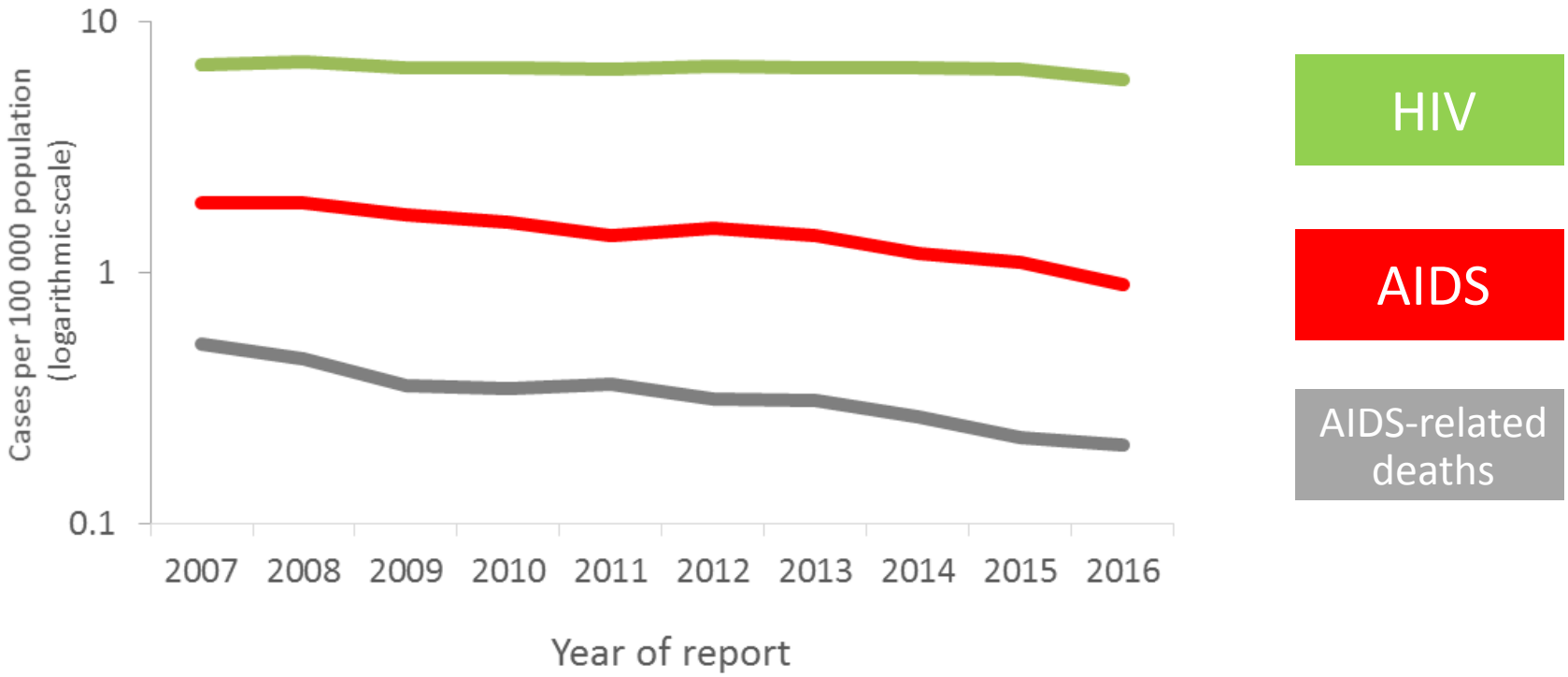


Figure 6. Percentage of people on treatment reaching viral suppression in 31 countries of Europe and Central Asia, 2016[24]



HIV diagnoses, AIDS diagnoses and AIDS-related deaths per 100 000 population, EU-EEA, 2007-2016



Deaths rates exclude countries not reporting deaths consistently over the period (Italy, Sweden)

Source: ECDC/WHO (2017). HIV/AIDS Surveillance in Europe 2017– 2016 data

THE PROBLEM OF LATE DIAGNOSIS

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A REPRESENTATIVE CASE

33 year-old woman comes to clinic to initiate care. Diagnosed HIV+ 3 month ago, but failed to link to care. History of malaise and chronic diarrhea. No other medical history. No other laboratory data is available.

- *What is the likelihood of a late presentation?*
- *When do you start antiretroviral treatment?*
  - *Obtain and wait for lab results?*
  - *Start today?*
- *Which ART regimen do you select?*

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WHAT IS LATE DIAGNOSIS?

Advanced HIV disease

- For adults, adolescents, and children ≥five years, advanced HIV disease is defined as a CD4 cell count <200 cells/mm^3 or a WHO clinical stage 3 or 4 event at presentation for care.
- All children with HIV younger than five years old should be considered as having advanced disease at presentation (for rationale, see section 2.2).
- A seriously ill adult or adolescent is defined as having any of the following danger signs: respiratory rate ≥30 breaths per minute; heart rate ≥120 beats per minute; or unable to walk unaided. Other clinical conditions, such as body temperature ≥39°C can also be considered based on local epidemiology and clinical judgement.
- A seriously ill child is defined as having any of the following danger signs: lethargy or unconsciousness; convulsions; unable to drink or breastfeed; and repeated vomiting. Other clinical conditions such as body temperature ≥39°C and age-defined tachycardia and/or tachypnoea can be considered based on clinical judgement.
- A severely immunosuppressed adult is defined as having a CD4 cell count <50 cells/mm^3.
- WHO Clinical Staging is a way to categorize HIV disease severity based on new or recurrent clinical events. There are 4 WHO clinical stages which range from mild symptoms (WHO clinical stage 1) to severe symptoms (WHO clinical stage 4).

WHO 2017

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THE PROBLEM ON LATE DIAGNOSIS

- Increased risk of:
  - Opportunistic infections and malignancies
  - Multiple illness at presentation
  - Hospitalization
  - Death
- Increased cost of care
  - In Canada, first year costs $14,790 vs $6764
  - 15X increase in hospital expenses
  - Decrease in cost-effectiveness

Enrico, Sabin, Monforte, JAIDS 2007

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HOW COMMON IS LATE PRESENTATION?

Country	Author, year	Definition	Prevalence
Australia	Hocking et al., 2000[10]	< 8 Weeks from diagnosis to AIDS event	249/1021 (24%)
Spain	Castilla et al., 2002[11]	HIV-positive test in the same/preceding month as AIDS event	8499/30778 (28%)
United States	Klein et al., 2003[12]	CD4 < 200 cells/μl	167/388 (43%)
Scotland	Manavi et al., 2004[13]	CD4 < 200 cells/μl	249/1021 (24%)
Canada	Krentz et al., 2004[14]	CD4 < 200 cells/μl	93/241 (39%)
Italy	Girardi et al., 2004[15]	CD4 < 200 cells/μl or AIDS in preceding month	379/968 (39%)
UK	Sabin et al., 2004[16]	CD4 < 50 cells/μl	110/719 (15%)
UK and Ireland	Sullivan et al., 2005[17]	CD4 < 200 cells/μl	301/977 (33%)

Enrico, Sabin, Monforte, JAIDS 2007

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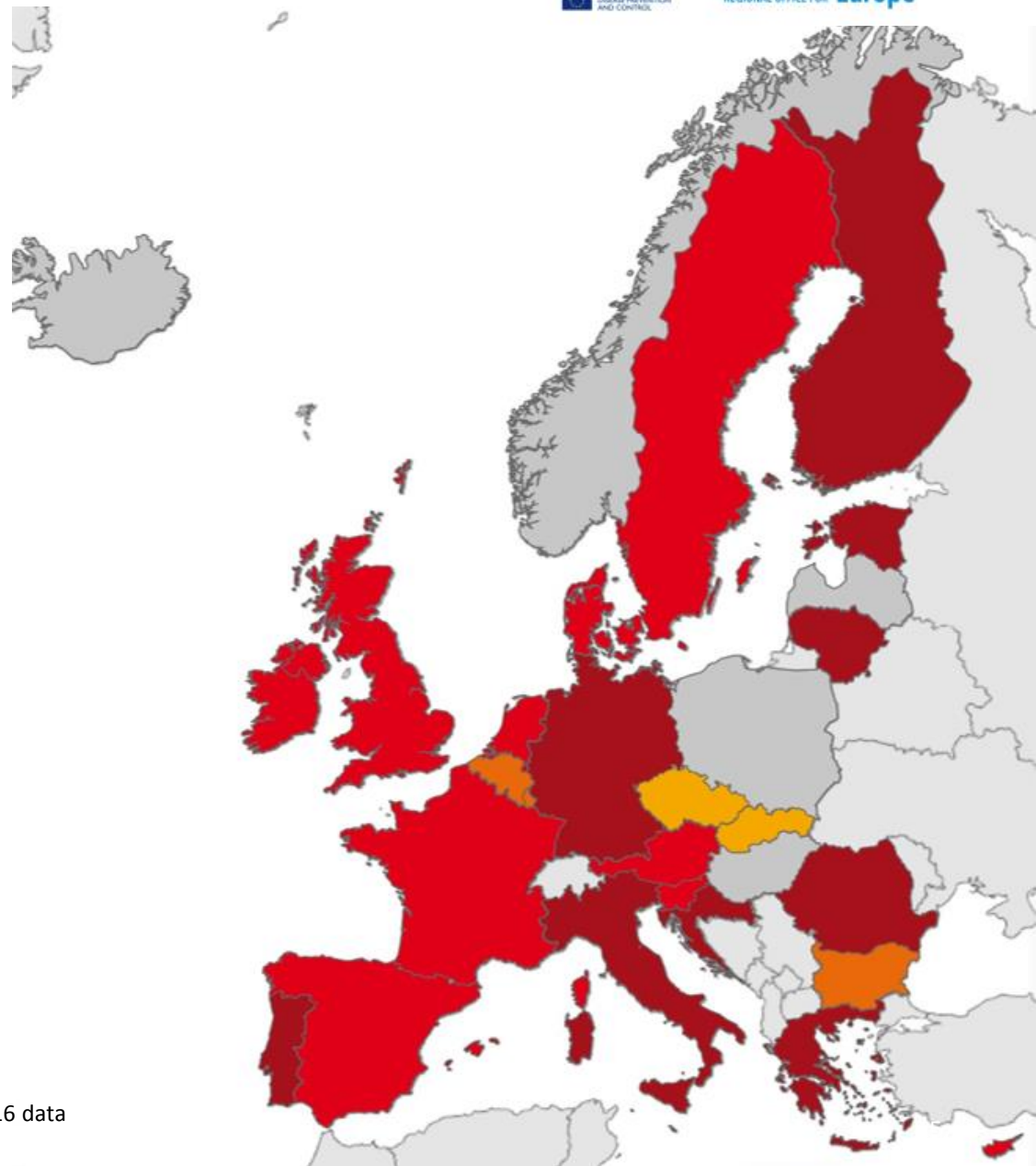
Late diagnosis, 2016, EU/EEA

% persons with CD4 <350 cells/mm³ at HIV diagnosis

- <30%
- 30 to <40%
- 40 to <50%
- >50%
- Missing data or did not report



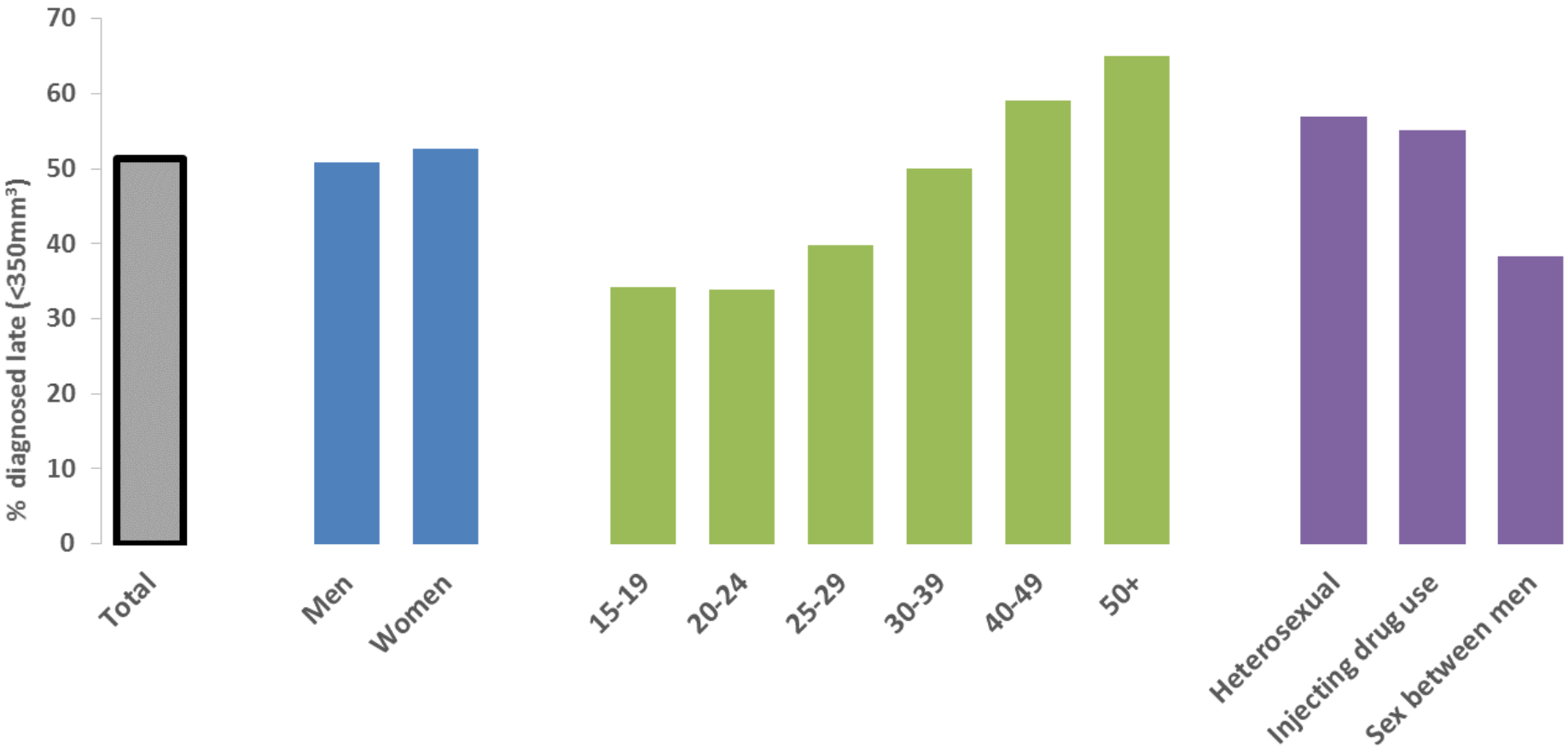
EU/EEA Average: 48%

Non-visible countries

- Luxembourg
- Malta

Source: ECDC/WHO (2017). HIV/AIDS Surveillance in Europe 2017– 2016 data

Proportion of persons diagnosed late*, by demographic, WHO European Region, 2016



*Diagnosed late=CD4<350 cells/mm^3 at diagnosis

Source: ECDC/WHO (2017). HIV/AIDS Surveillance in Europe 2017– 2016 data

OPTIMIZING THE CARE CONTINUUM

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OPTIMIZING THE HIV CARE ENVIRONMENT

- Laws that criminalize the conduct of MSM, transgender individuals, substance users, and sex workers are not recommended [A IV]
- Laws that criminalize the conduct of PLHIV based on perceived exposure to HIV are not recommended [A IV]
- HIV-related restrictions on entry, stay, and residence in any country for PLHIV are not recommended [A IV]
- Strategies to monitor for/eliminate race-, ethnicity-, gender-, age-, sexual orientation-, and/or behavior-based stigma and discrimination are recommended [B II]

IAPAC Guidelines for Optimizing the HIV Care Continuum. IAPAC Panel, 2015

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INCREASING HIV TESTING COVERAGE & LINKAGE TO CARE

- Routinely offer opt-out HIV testing to all individuals who present at health facilities is recommended [A I]
- Community-based HIV testing is recommended to reach populations less likely to access facility-based testing [A I]
- HIV self-testing is recommended with provision of guidance about proper test administration and direction on what to do once the test result has been obtained [B II]
- Use of epidemiological data is recommended to expedite identification of at-risk individuals for HIV testing purposes [B II]

IAPAC Guidelines for Optimizing the HIV Care Continuum. IAPAC Panel, 2015

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INCREASING HIV TESTING COVERAGE & LINKAGE TO CARE (CONTINUED)

- The offer of HIV testing to partners of newly diagnosed individuals is recommended [A I]
- Immediate referral to HIV care is recommended following an HIV-positive diagnosis to improve linkage to ART [A I]
- For high-risk individuals who test HIV negative, offering PrEP is recommended in addition to free condoms, risk reduction education, and PEP [A I]
- The use of case managers and patient navigators to increase linkage to care is recommended [B II]

IAPAC Guidelines for Optimizing the HIV Care Continuum. IAPAC Panel, 2015

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WHEN TO START ART

ANTIRETROVIRAL THERAPY WORKS: TREATMENT FOR TREATMENT

- Prevents disease progression
- Restores immune health
- Early treatment:
  - Reduced death
  - Reduced cancer
  - Reduced tuberculosis

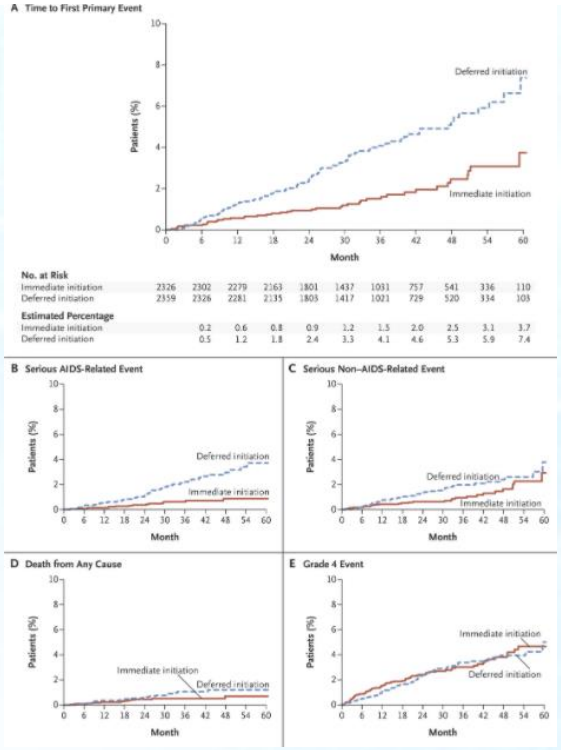
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group

N Engl J Med 2015; 373:795-807 | August 27, 2015 | DOI: 10.1056/NEJMoa1506816



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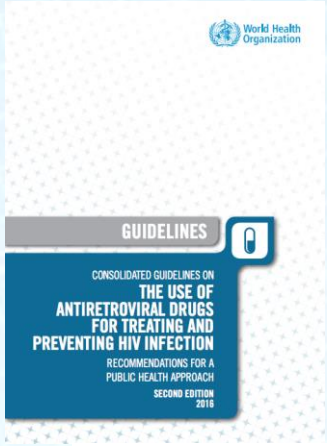

4.3.1 When to start ART in adults (>19 years old)

Recommendation

- **ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count (strong recommendation, moderate-quality evidence).**

NEW

- As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤350 cells/mm³ (strong recommendation, moderate-quality evidence).

World Health Organization, 2015

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EACS European AIDS Clinical Society

GUIDELINES

Version 9.0
October 2017

English

ART is recommended in all adults with chronic HIV infection, irrespective of CD4 counts[i]

i ART should always be recommended irrespective of the CD4 count, but the lower the CD4 count, the greater the urgency to start ART immediately. Use of ART should also be recommended at any CD4 count in order to reduce sexual transmission and mother-to-child transmission of HIV (before third trimester of pregnancy).

- For best timing for starting ART in persons with tuberculosis and cryptococcal meningitis, see page 16 and page 89.
- A possible exception could be persons with high CD4 counts and HIV-VL < 1000 copies/mL, although even in such persons ART initiation has been shown to increase CD4 count, dampen inflammation and lower the risk of emerging infection with higher HIV-VL.
- Genotypic resistance testing is recommended prior to initiation of ART, ideally at the time of HIV diagnosis; otherwise before initiation of ART.
- If ART needs to be initiated before genotypic testing results are available, it is recommended to include a drug with a high genetic barrier to resistance in the first-line regimen (e.g. a PI/r, PI/c or DTG). Ideally, before starting treatment, the HIV-VL level and CD4 count should be repeated to more reliably assess the infection status and subsequent response to ART.

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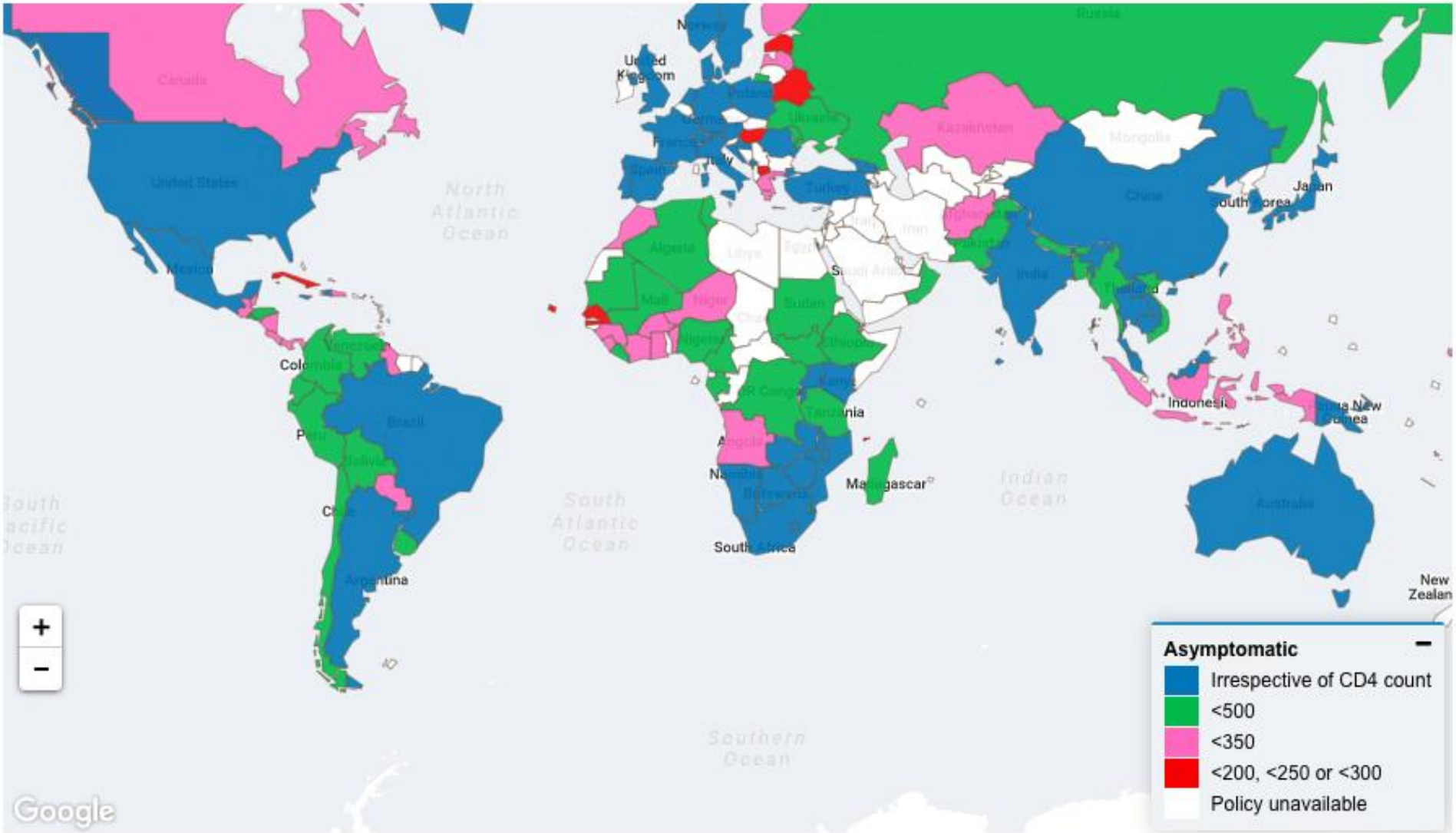
ART eligibility criteria for asymptomatic people living with HIV

June 15, 2017



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SAME DAY ART?

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INCREASING TREATMENT COVERAGE

Offer immediate ART, irrespective of CD4 count [A I]

First-line ARV regimens with the highest levels of efficacy, lowest adverse event profiles, and delivered in fixed-dose, once-daily dosed combinations are recommended [B II]

Embrace plasma VL (at least every 6 months) as preferred monitoring metric [B II]

HIV drug resistance testing is recommended at entry into care or prior to ART initiation, and when virologic failure is confirmed [BI]

- **Where routine access to HIV drug resistance testing is restricted, population-based surveillance is recommended**

Community-located ART distribution is recommended [A II]

IAPAC Guidelines for Optimizing the HIV Care Continuum. IAPAC Panel, 2015

SAME-DAY ART INITIATION

- Advantages
  - Improved linkage/retention in care
  - Decreased morbidity
  - Lower risk of transmission
- Disadvantages
  - Lack of baseline laboratory data (HBV, renal disease, drug resistance)
  - IRIS
    - ?risk with INSTIs
  - Lack of willingness (coercion)
  - Logistical complexity

SAME-DAY ART: CLINICAL TRIALS

- Randomized trials at individual level
  - Haiti study (Koenig)
  - CASCADE Study (Lesotho)
  - RapIT (South Africa, Rosen et al.)
- Randomized trial at clinic level
  - START-ART (Uganda, Geng et al.)
- Non-randomized trial
  - RAPID protocol (San Francisco, Pilcher et al.)

PLOS | MEDICINE

Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: A randomized unblinded trial

Table 2. Study outcomes by group.

Outcome	Standard ART Group ($n = 356$)	Same-Day ART Group ($n = 347$)	Unadjusted Risk Difference (95% CI)	*p*-value
Primary Outcome				
Retained in care at 12 months with VL <50 copies/ml	156 (43.8%)	184 (53.0%)	9.2% (1.8%, 16.6%)	0.015†
Secondary Outcomes				
Retained in care at 12 months with VL <1,000 copies/ml	184 (51.7%)	212 (61.1%)	9.4% (2.1%, 16.7%)	0.012‡
Retained in care at 12 months, regardless of VL results	256 (71.9%)	277 (79.8%)	7.9% (1.6%, 14.2%)	0.014††
Died	20 (5.6%)	10 (2.9%)		
Lost to follow-up	80 (22.5%)	60 (17.3%)		

† *p*-value comparing the proportion of all patients who were retained in care with viral load <50 copies/ml between the 2 arms.

‡ *p*-value comparing the proportion of all patients who were retained in care with viral load <1,000 copies/ml between the 2 arms.

†† *p*-value comparing the proportion of all patients who were retained in care between the 2 arms.

ART, antiretroviral therapy; VL, viral load.

https://doi.org/10.1371/journal.pmed.1002357.t002

Koenig, et al., PLOS Medicine 2017

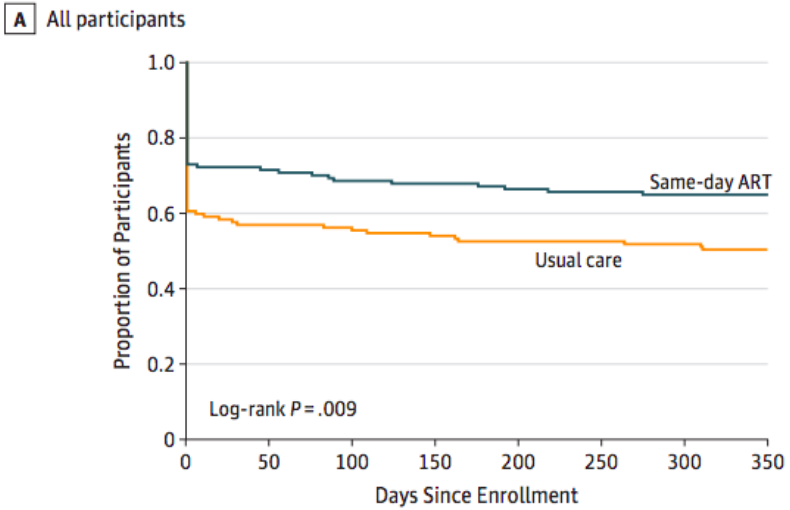
JAMA | Original Investigation

Effect of Offering Same-Day ART vs Usual Health Facility Referral During Home-Based HIV Testing on Linkage to Care and Viral Suppression Among Adults With HIV in Lesotho

The CASCADE Randomized Clinical Trial

- Randomized study of same-day test and ART initiation during routine home-based testing program
- Same-day (n=138) vs standard initiation in health facility (n=140)
- Same-day ART initiation significantly improved linkage to care at 3 months (69% vs 43%) and 12 month viral suppression (50% vs 34%).

Figure 2. Kaplan-Meier Curves for Retention in Care



No. at risk

Same-day ART	137	98	94	93	91	90	89	86
Usual care	137	78	77	74	72	72	71	64

Labhardt, et al., JAMA 2018

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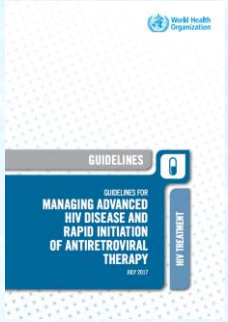
SAME-DAY ART: EVIDENCE SUMMARY

- 3 large randomized studies in different contexts have generally consistent results: more suppression, same or better retention in care, same or better survival
  - Pre-ART care can be dramatically simplified
  - Even easier if CD4 result not needed
- Long-term safety and outcomes are not known
- Promising, but very limited data in high-resource countries



WHO RECOMMENDATIONS

Rapid initiation of antiretroviral therapy

Rapid ART initiation[a] should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment.

(Strong recommendation: high-quality evidence for adults and adolescents; low-quality evidence for children)

[a]Rapid initiation is defined as within seven days from the day of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation.

ART initiation should be offered on the same day to people who are ready to start.

(Strong recommendation: high-quality evidence for adults and adolescents; low-quality evidence for children)

WHO, July 2017

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World Health Organization

In 2016, WHO included DTG-based HIV treatment as an alternative first-line regimen. Clinical trials show that DTG is more effective, better tolerated and more protective against treatment discontinuation from adverse drug reactions than efavirenz (EFV) at standard dose (600 mg/day) and boosted (PIs).[1] Further, DTG is associated with fewer drug interactions, has a higher genetic barrier to resistance, and is being launched as a low-cost, once-daily generic formulation for low- and middle-income countries.

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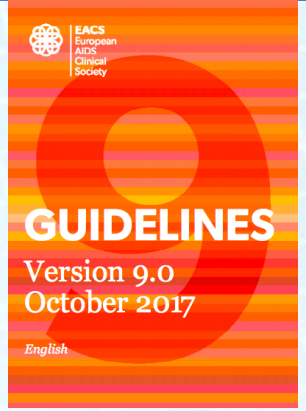

ART is recommended in all adults with chronic HIV infection, irrespective of CD4 counts[i]

- If ART needs to be initiated before genotypic testing results are available, it is recommended to include a drug with a high genetic barrier to resistance in the first-line regimen (e.g. a PI/r, PI/c or DTG). Ideally, before starting treatment, the HIV-VL level and CD4 count should be repeated to more reliably assess the infection status and subsequent response to ART.

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IRIS and INSTIs
REALITY Trial

Design

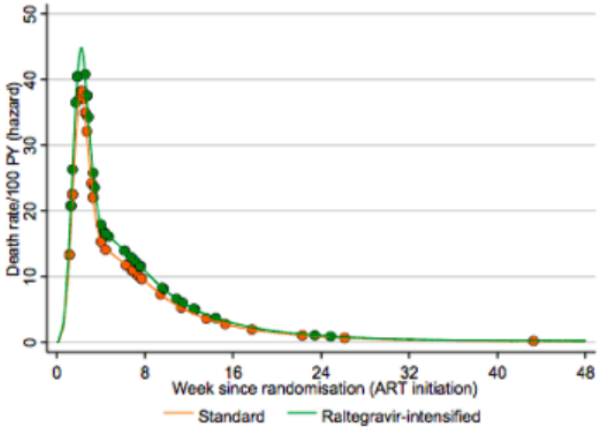
- 1805 ART-naïve HIV-infected adults, adolescents & children ≥5 years with CD4<100 cells/µl

1:1 randomisation

- **Initiate ART with 2NRTI +NNRTI+12 weeks additional raltegravir**
- **Initiate ART with 2NRTI +NNRTI alone (standard of care)**

- Follow-up to week 48
  - Safety bloods at screening, weeks 4 and 48; FBC & CD4 at weeks 0, 12, 24, 36, 48; Viral loads retrospectively at weeks 0, 4, 12, 24, 48
- **Primary endpoint: 24-week mortality**
- Two other factorial randomisations investigated
  - 12 weeks enhanced prophylaxis (Hakim *et al.*, NEJM 2017)
  - 12 weeks supplementary food (Mallewa *et al.*, CROI 2017)
- ISRCTN43622374

Incidence of fatal IRIS-compatible events



36 (4.0%) RAL vs 31 (3.4%) standard experienced fatal IRIS (p=0.54), occurring a median 4.4 (IQR 2.6-9.4) weeks after ART initiation

Gibb, CROI 2018, Boston

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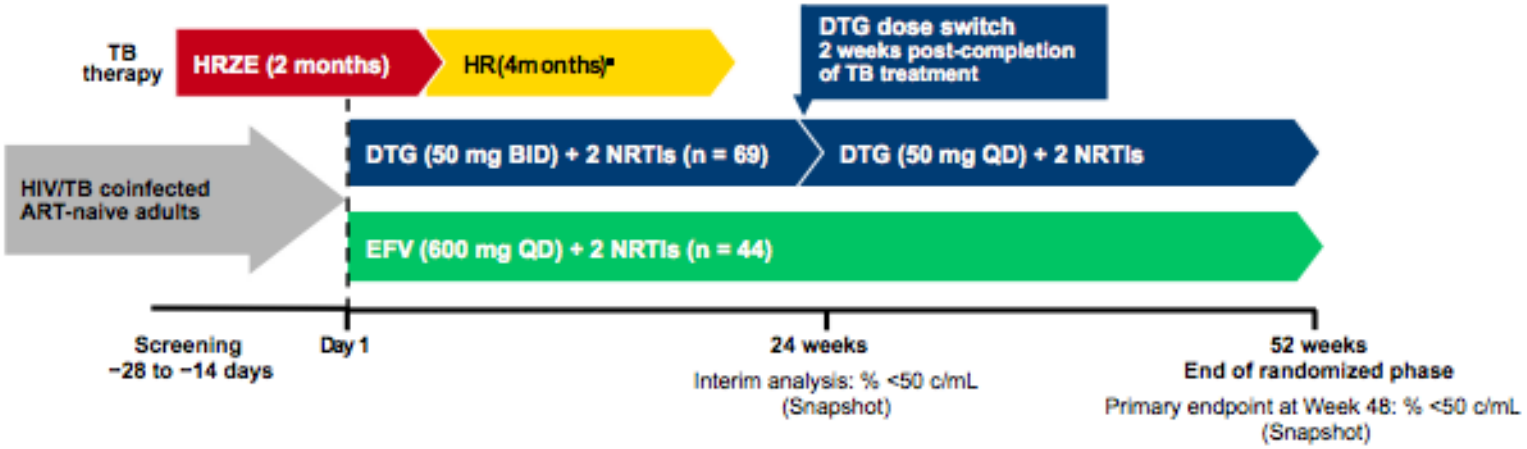
INSPIRING: Phase IIIb Study Design

Phase IIIb, randomized, multicenter, open-label, non-comparative, active-control parallel-group study



Inclusion criteria
- HIV-1 RNA ≥1000 copies/mL and CD4+ ≥50 cells/mm³
- Pulmonary, pleural, or lymph node tuberculosis with RIF-sensitive MTB confirmed by culture or GeneXpert
- RIF-containing TB treatment started up to a maximum of 8 weeks before randomization and no later than the screening date

DTG:EFV 3:2 randomization stratified by
- Screening plasma HIV-1 RNA ≤100,000 or >100,000 copies/mL
- Screening CD4+ ≤100 cells/mm³ or >100 cells/mm³

ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; HR, isoniazid, rifampin; HRZE, isoniazid, rifampin, pyrazinamide, ethambutol; NRTI, nucleoside reverse transcriptase inhibitor; RIF, rifampin; TB, tuberculosis.
*Duration of continuation phase of TB treatment according to local guidelines (continuation phase up to 7 months in some countries).
ClinTrials.gov NCT02178592

Dooley et al. CROI 2018; Boston, MA.

INSPIRING: Phase IIIb Study

Participants With TB and Non–TB-Associated IRIS

n (%)	DTG (n=69)	EFV (n=44)
Participants with events sent to adjudication committee for TB-associated IRIS	9 (13)	12 (27)
Met criteria for TB-associated IRIS	4[a] (6)	4[b] (9)
Possibly met criteria for TB-associated IRIS	0	0
Participants with events sent to adjudication committee for non–TB-associated IRIS	2 (3)	3 (7)
Met criteria for non-TB-associated IRIS	1[c] (1)	0
Possibly met criteria for non-TB-associated IRIS	1[d] (1)	0

No participant in either arm permanently discontinued treatment due to IRIS

[a]1 x Grade 1, 2 x Grade 2 and 1 x Grade 3.
[b]3 x Grade 2 and 1 x Grade 4.
[c]Grade 2 (IRIS and strongyloidiasis; also experienced TB-associated IRIS).
[d]Grade 1 (Herpes zoster).

Dooley et al. CROI 2018; Boston, MA.

A REPRESENTATIVE CASE

33 year-old woman recently diagnosed HIV+, 3 month history of malaise and chronic diarrhea.

- *Patient initiates same-day ART with TAF/FTC + DTG*
- *CD4 was later found to be 20 c/mm^3; HIV RNA 501,000 c/mm^3*
- *1 month later:*
  - *Malaise is markedly improved*
  - *Diarrhea is resolved*
  - *CD4 is 99 c/mm^3; HIV RNA 351 c/mm^3*

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LATE DIAGNOSIS AND SAME-DAY ART INITIATION

- Late diagnosis is common among people living with HIV in Europe
- Optimizing the care continuum (testing, linkage/retention in care) key
- ART is recommended for all
- Growing evidence supports rapid and/or same-day initiation of ART

Questions?

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