AETC AIDS Education & Training Center Program Mountain West

AIDS Clinical Conference: Care of the Newly Diagnosed Patient

Jehan Budak, MD
Acting Assistant Professor
Division of Allergy & Infectious Diseases
University of Washington

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Disclosures

No conflicts of interest or relationships to disclose.

Objectives

1. Discuss rates of transmitted drug resistance and its impact on baseline resistance testing

2. Discuss data for same-day ART start

3. Describe the 2019 updates to the DHHS ART guidelines and interpret the data regarding DTG/3TC

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Roadmap

- Transmitted Drug Resistance
- Same-Day ART Start
- ART Options to Start

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Roadmap

- Transmitted Drug Resistance
- Same-Day ART Start
- ART Options to Start

Transmitted Drug Resistance (TDR)

- The transmission of an ART-resistant HIV virus from a person with HIV to a person who does not have HIV

- How much transmitted drug resistance do we see?

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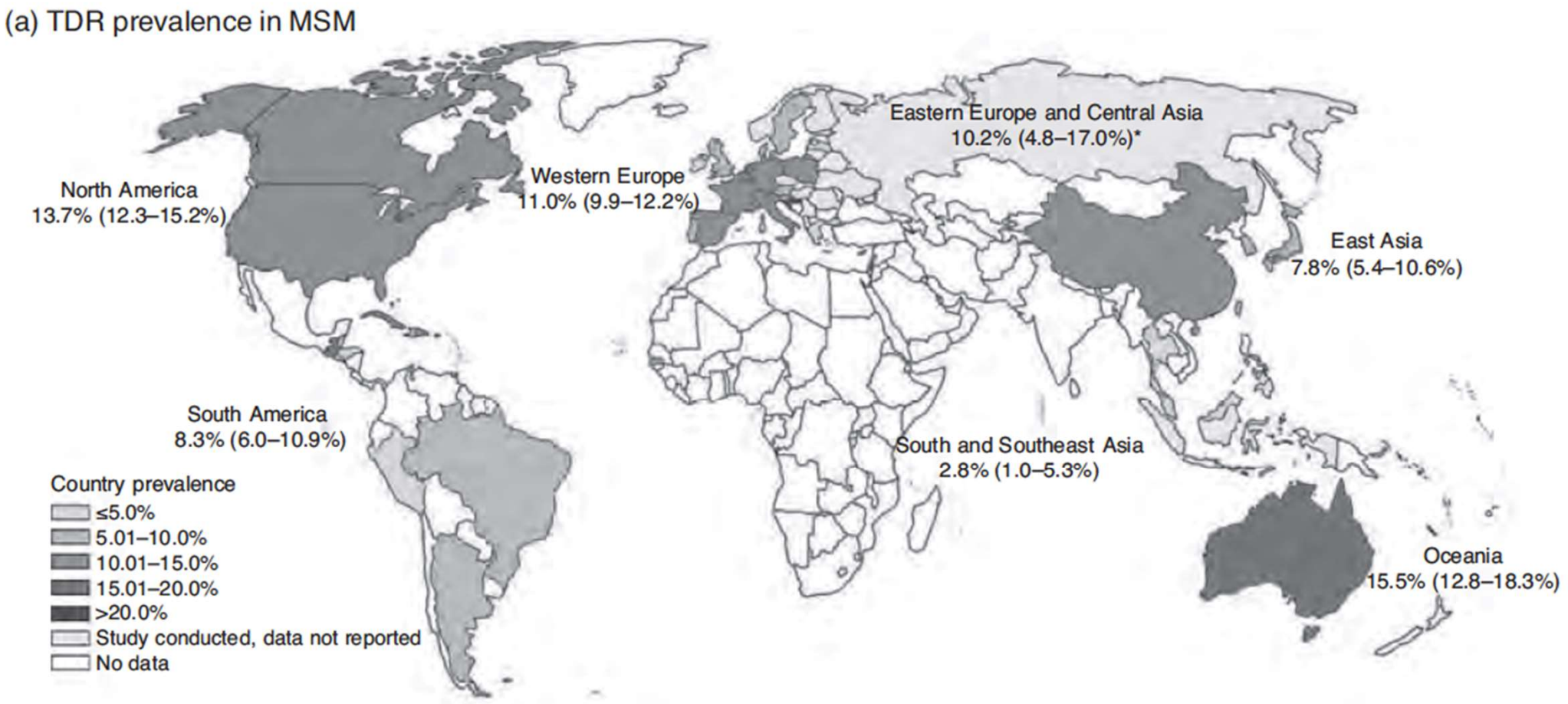
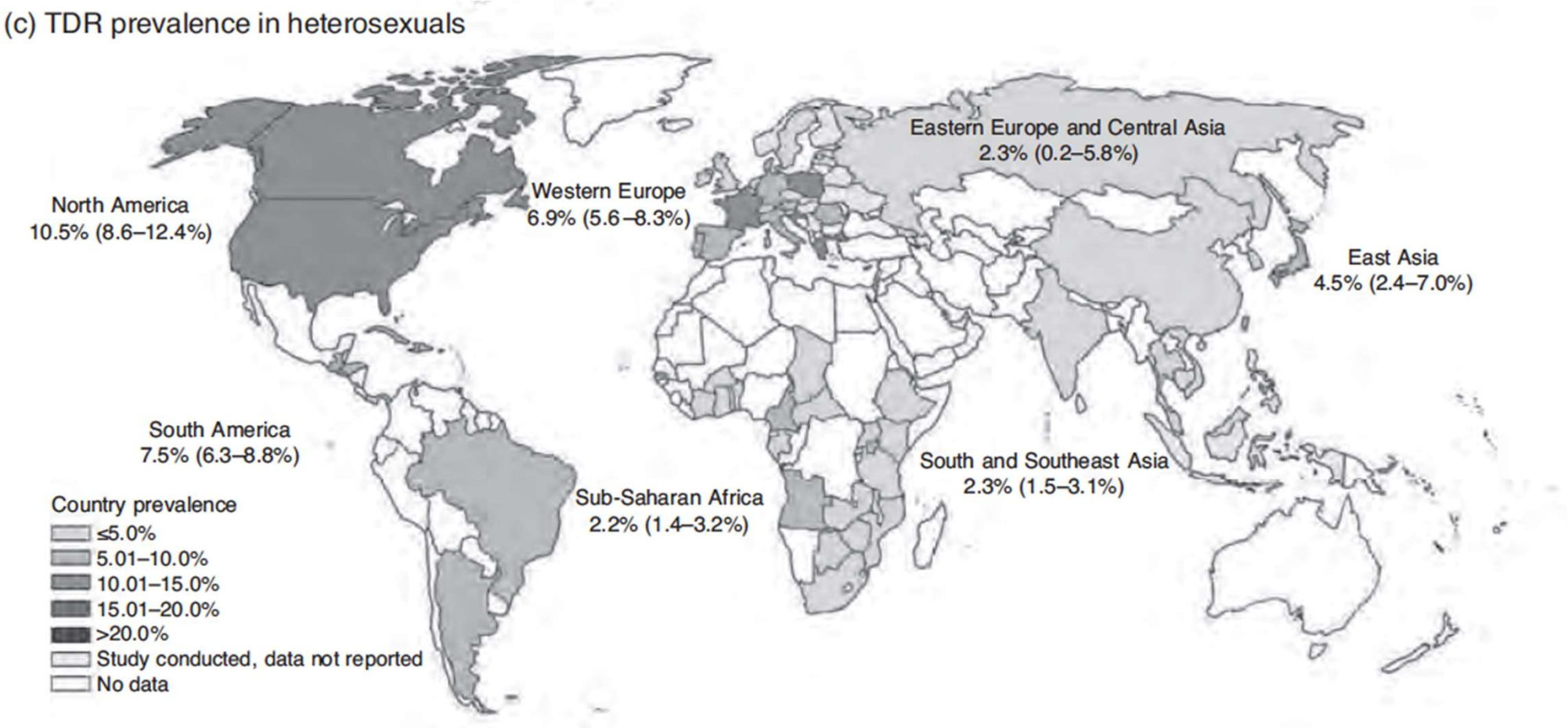
Transmitted Drug Resistance Worldwide, 1999-2013



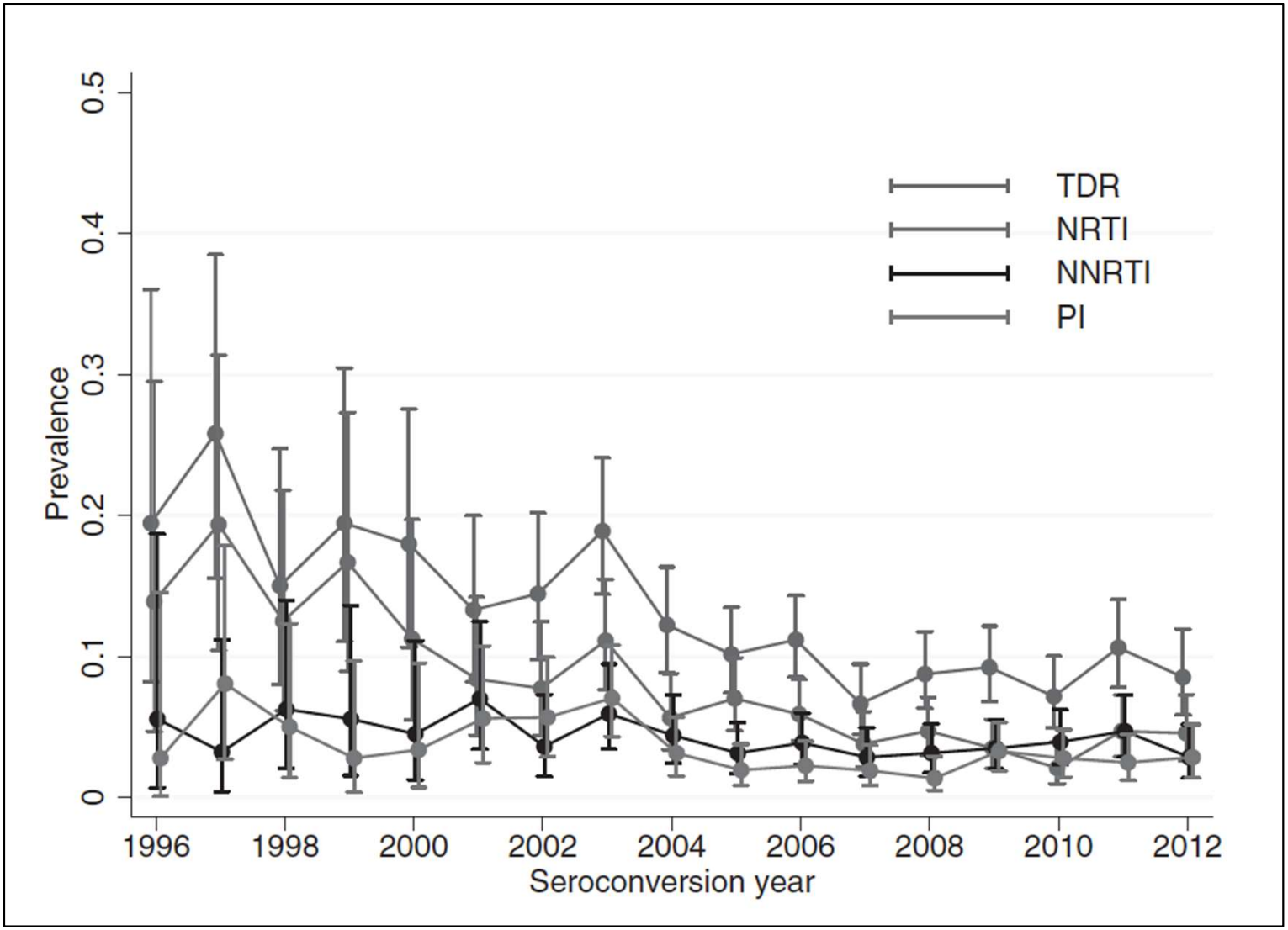
Pham, AIDS 2018.

Transmitted Drug Resistance Worldwide, 1999-2013



Pham, AIDS 2018.

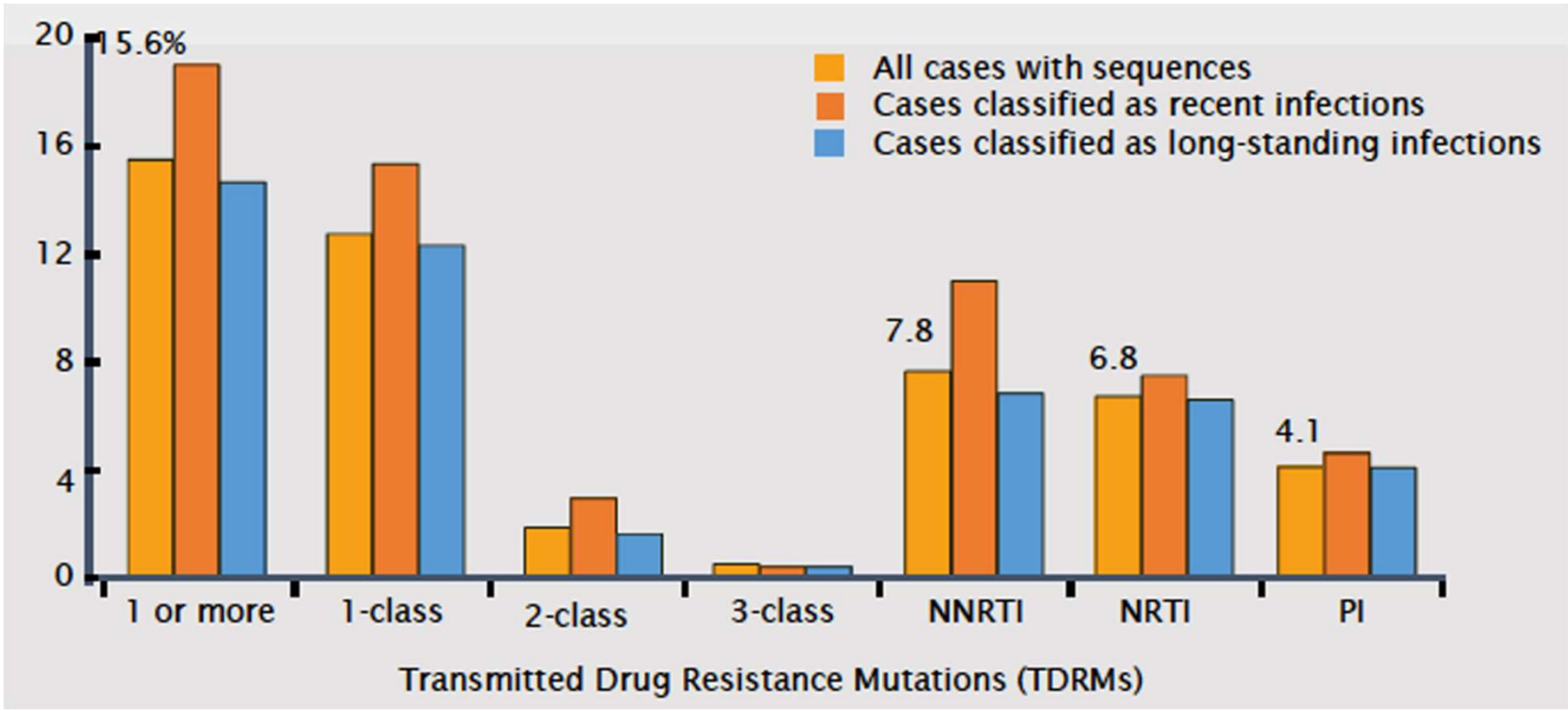
Temporal Trends in TDR in Europe, 1996-2012



Olson, AIDS 2018.

Transmitted Drug Resistance in US, 2006-2009

Genotypic analysis of samples from newly diagnosed patients in CDC National HIV Surveillance System (N = 12,668)



Ocfemia MCB, CROI 2012 #730

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#1 - Audience Response Question

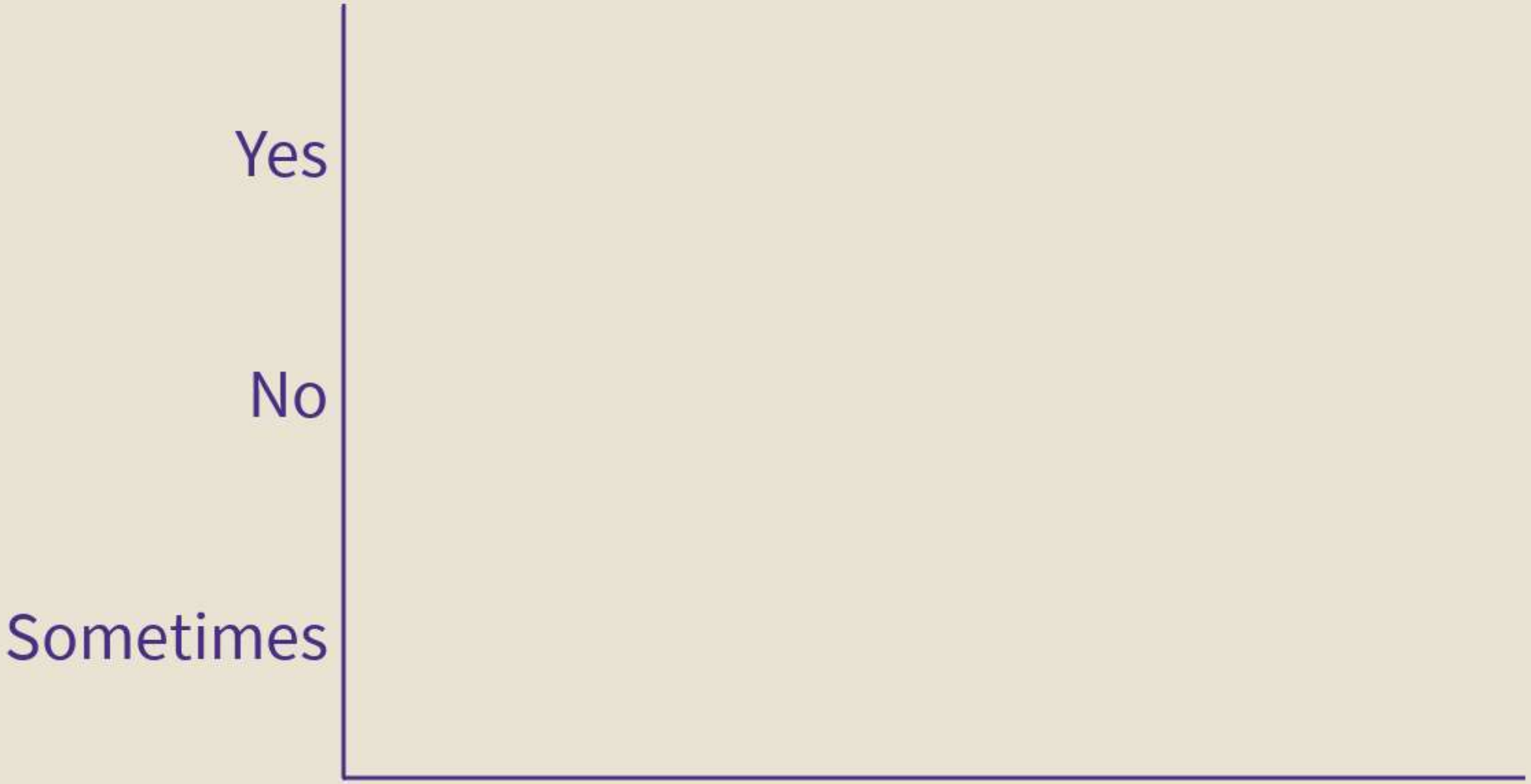
Do you routinely order a baseline integrase genotype?

A. Yes

B. No

C. Sometimes

Do you routinely order a baseline integrase genotype?



DHHS Guidelines: HIV Drug-Resistance Testing

For Antiretroviral Therapy-Naive Persons:

- HIV drug-resistance testing is recommended at entry into care for persons with HIV to guide selection of the initial antiretroviral therapy (ART) regimen **(AII)**. If therapy is deferred, repeat testing may be considered at the time of ART initiation **(CIII)**.
- Genotypic, rather than phenotypic, testing is the preferred resistance testing to guide therapy in antiretroviral (ARV)-naive patients **(AIII)**.
- In persons with acute or recent (early) HIV infection, in pregnant people with HIV, or in people who will initiate ART on the day of or soon after HIV diagnosis, ART initiation should not be delayed while awaiting resistance testing results; the regimen can be modified once results are reported **(AIII)**.
- Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers should ensure that genotypic resistance testing also includes the integrase gene **(AIII)**.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Accessed 2/16/2020.

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DHHS Guidelines: HIV Drug-Resistance Testing

- HIV drug-resistance testing is recommended at entry into care for persons with HIV to guide selection of the initial antiretroviral therapy (ART) regimen (AII).
- In persons with acute or recent (early) HIV infection, in pregnant people with HIV, or in people who will initiate ART on the day of or soon after HIV diagnosis, ART initiation should not be delayed while awaiting resistance testing results; the regimen can be modified once results are reported (AIII).
- Standard genotypic drug-resistance testing in ARV-naïve persons involves testing for mutations in the RT and PR genes. If transmitted INSTI resistance is a concern…ensure that genotypic resistance testing also includes the integrase gene (AIII).

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Accessed 2/16/2020.

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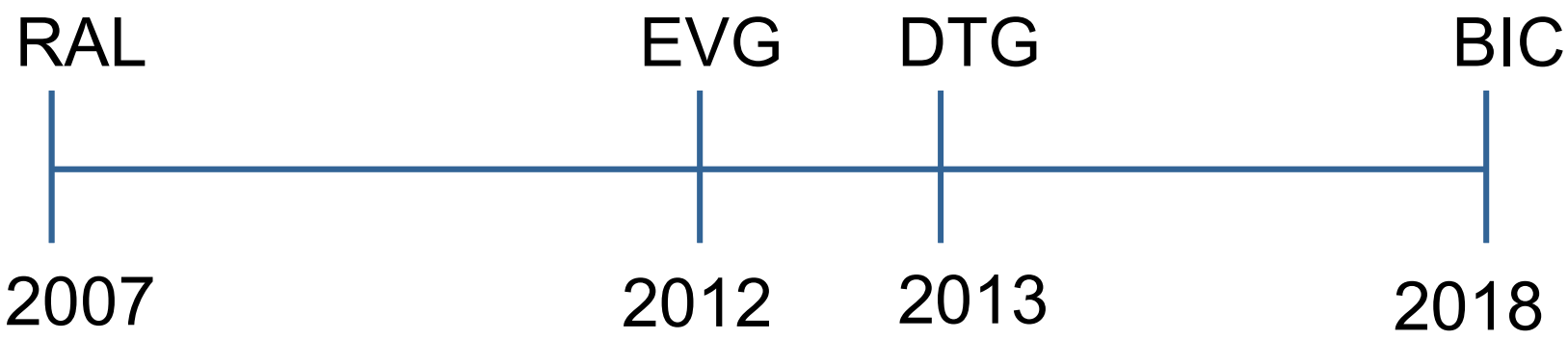
INSTI FDA Approval Timeline



Is Transmitted INSTI Resistance a Concern?

- UK cohort of 101 ART-naïve (2010-2013)[1]
  - No major INSTI TDR was detected
- US cohort of 82 ART-naïve (2005-2013)[2]
  - No baseline INSTI-R was detected
- Santa Clara County cohort of 206 ART-naïve (2006-2013)[3]
  - Overall TDR prevalence 17.5% (36/206)
  - One INSTI TDR (E138A) was detected
- Swiss Cohort of 1316 ART-naïve (2008-2014)[4]
  - One INSTI TDR (T66I) was detected (1/1316 (0.08%))

1-Tostevin, HIV Med 2017. 2-Stekler, Antivir Ther 2015. 3-Chan, Heliyon 2019. 4-Scherrer, JID 2016.

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Case Reports of Transmitted INSTI Resistance

1. Transmitted RAL resistance[1]
   - INSTI GT showed N155H, E157Q, and G163R
2. Transmitted multi-class drug resistance (Young)[2]
   - INSTI GT showed Q148H and G140S
3. Transmitted multi-class drug resistance (Volpe)[3]
   - INSTI GT showed Q148H and G140S
4. Baseline INSTI GT on a patient prescribed BIC/TAF/FTC[4]
   - E138A, G140S, and Q148H

1-Boyd, Antivir Ther 2011. 2-Young, Antivir Ther 2011. 3-Volpe, JIAPAC 2015. 4-McGee, OFID 2018.

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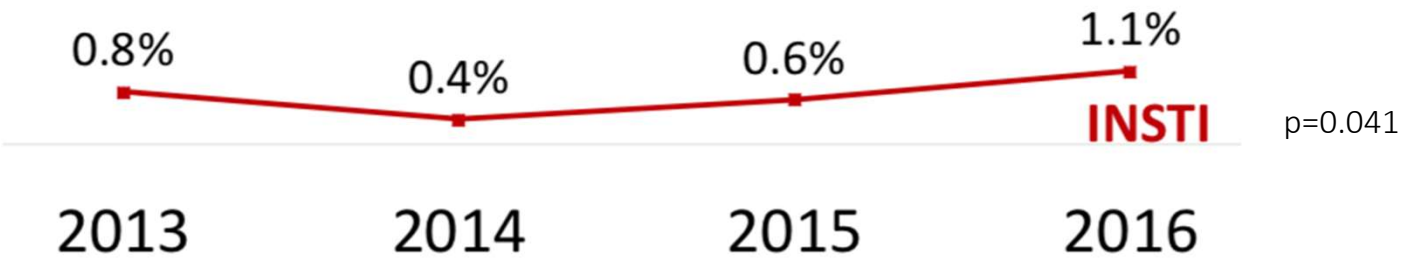
INSTI TDR in 23 US Jurisdictions, 2013-2016

- 6880/36288 (19%) cases with ≥ 1 TDRM
  - Of 5571 with INSTI results, 42 (0.8%) INSTI TDRM

- Overall TDR prevalence stable over 2013-2016
- What about INSTI TDR prevalence over 2013-2016?



McClung P, CROI 2019 #3337

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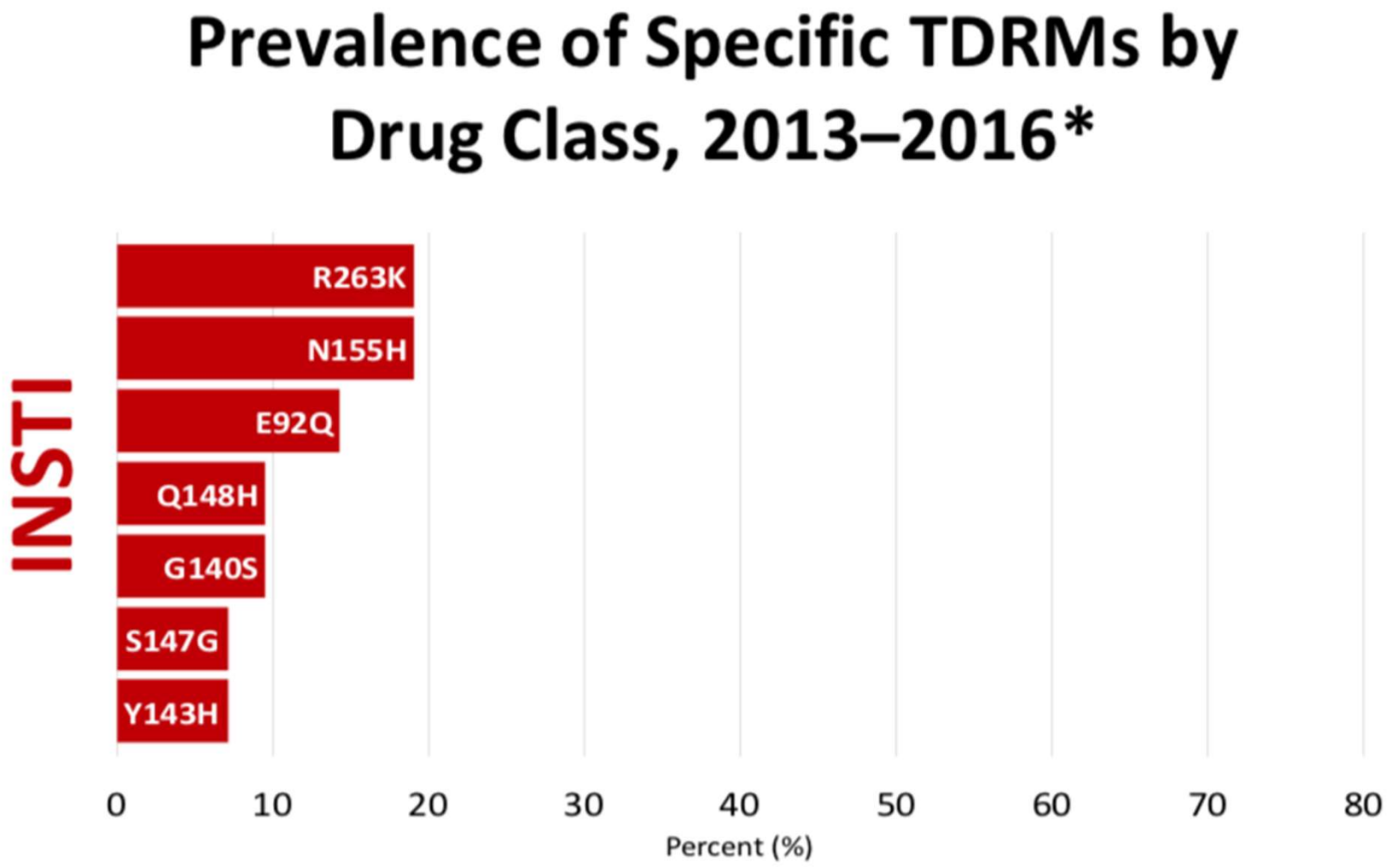
Common Mutations seen with INSTI TDR



McClung P, CROI 2019 #3337

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#2 - Audience Response Question

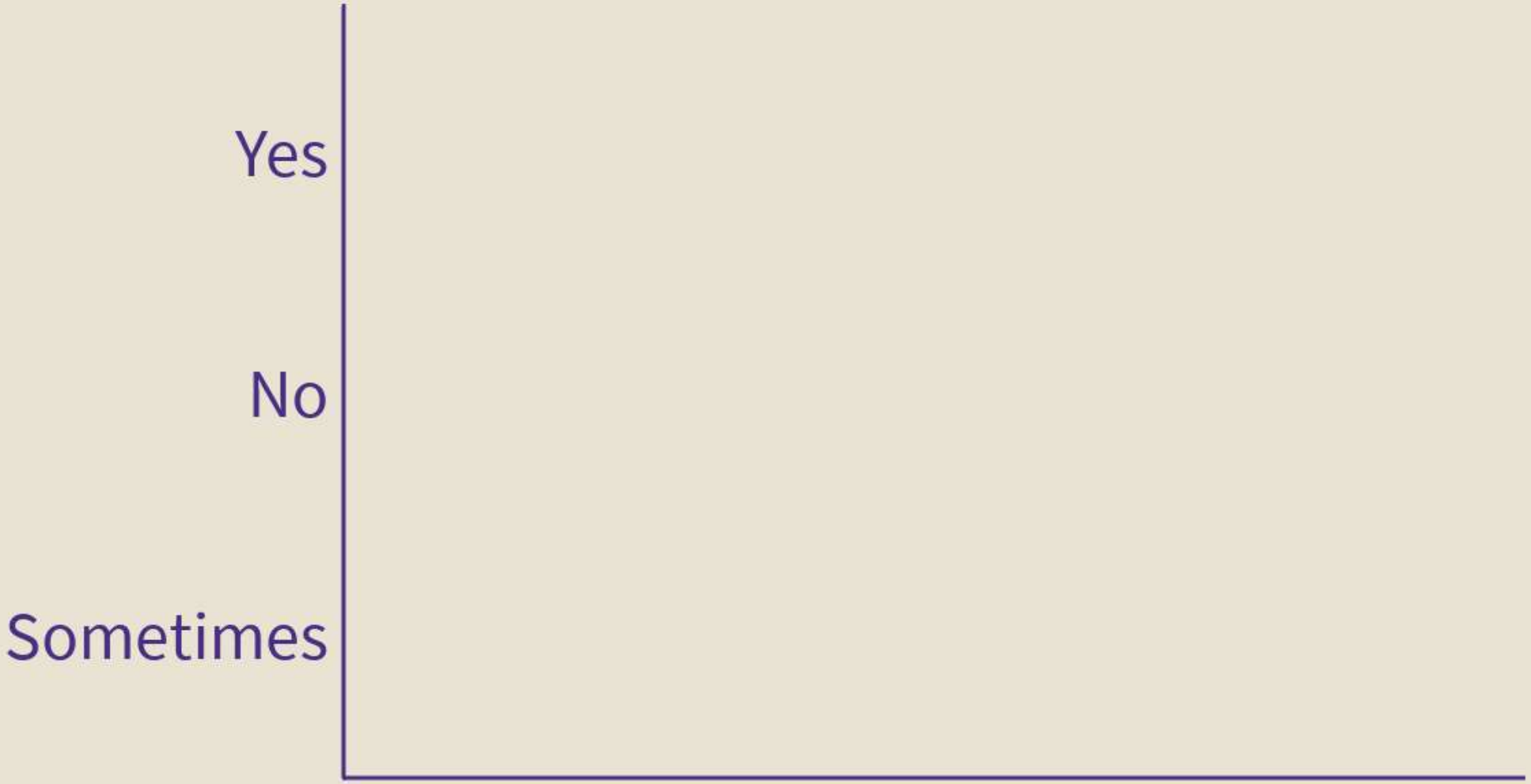
Will you order baseline integrase genotypes as your practice?

A. Yes

B. No

C. Sometimes

Will you order baseline integrase genotypes as your practice?



What about the cost-effectiveness of genotypes?

- Baseline INSTI-R testing modelling (2017)[1]
  - INSTI-R testing resulted in worse clinical outcomes compared to no IR testing and increased costs by 200 USD/person/year

- Baseline genotype modelling (2019)[2]
  - Compared to no baseline GT, baseline GT cost an additional 500 USD/person and was not cost-effective
  - With INSTI-based first-line regimens in the US, baseline GT offers minimal clinical benefit and is not cost effective

1-Koullias, CID 2017. 2-Hyle, CID 2019.

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Roadmap

- Transmitted Drug Resistance
- Same-Day ART Start
- ART Options to Start

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How Quickly to Start ART?

- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) recommends initiating ART at the time of diagnosis (when possible) or soon afterwards to increase the uptake of ART, decrease the time required to achieve linkage to care and virologic suppression, and improve the rate of virologic suppression among individuals who have recently received HIV diagnoses (AII).

- What data exist for same-day ART start?

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Accessed 2/16/2020.

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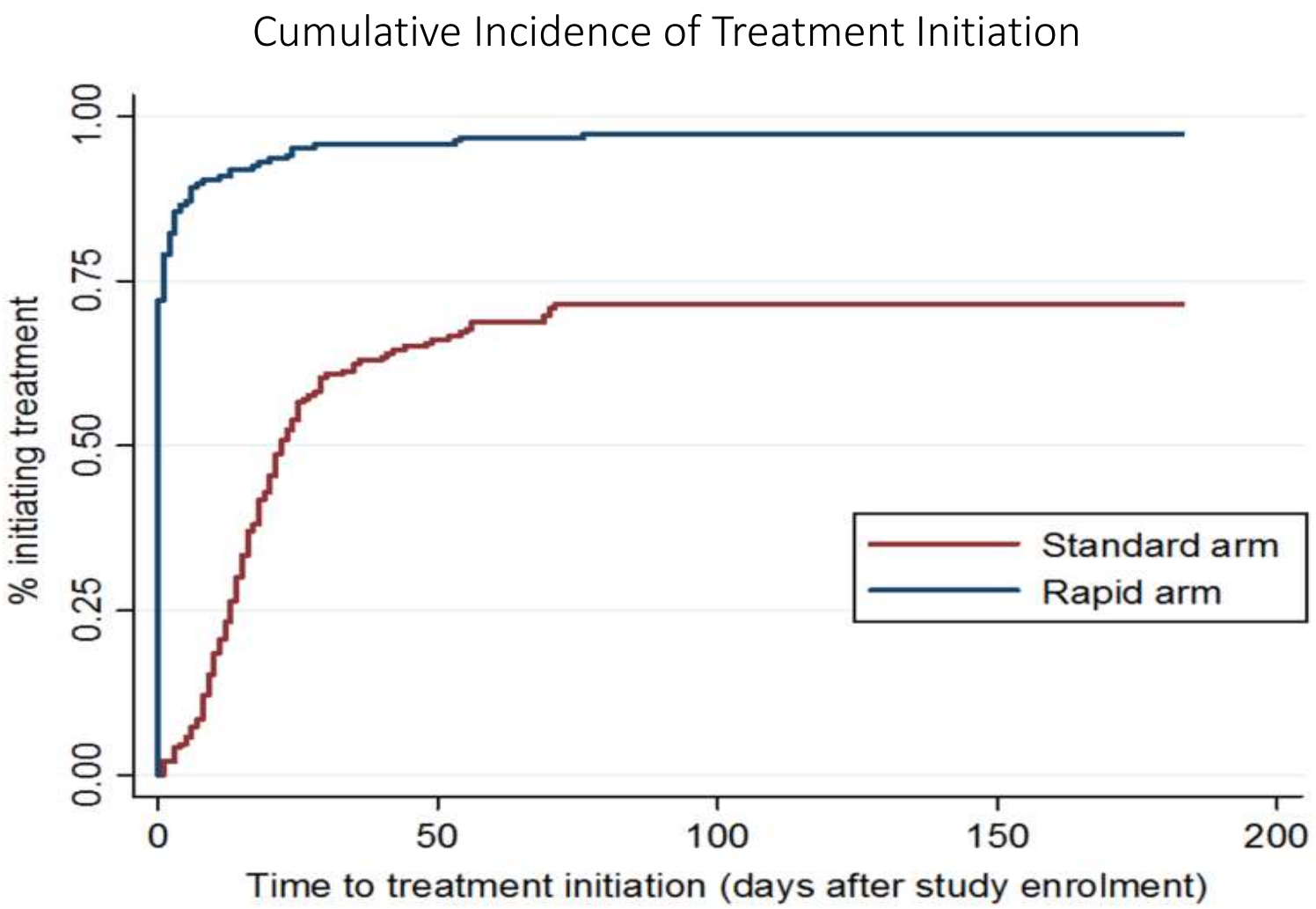
RapIT RCT in South Africa: Results



Rosen, PLoS Med 2016.

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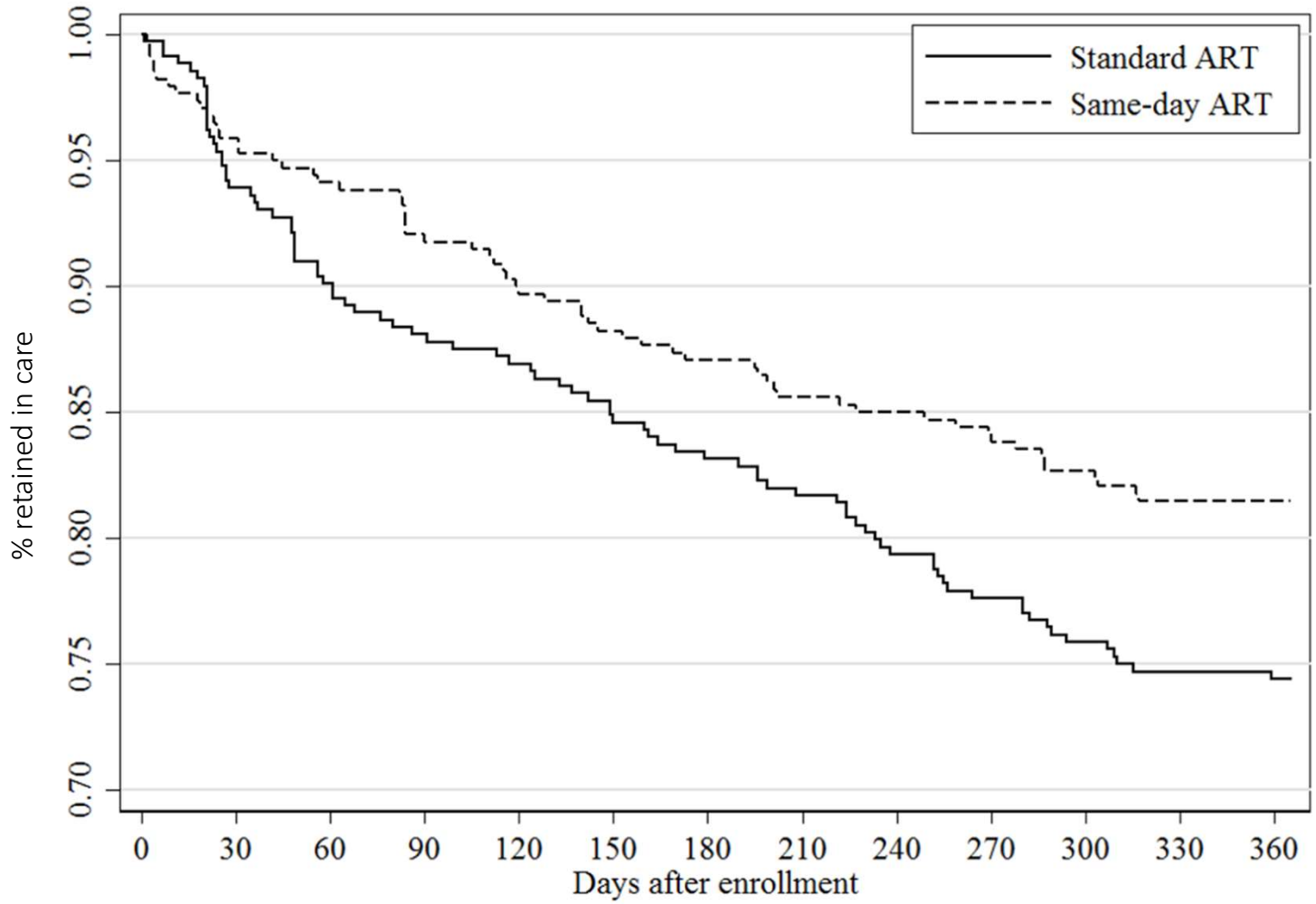
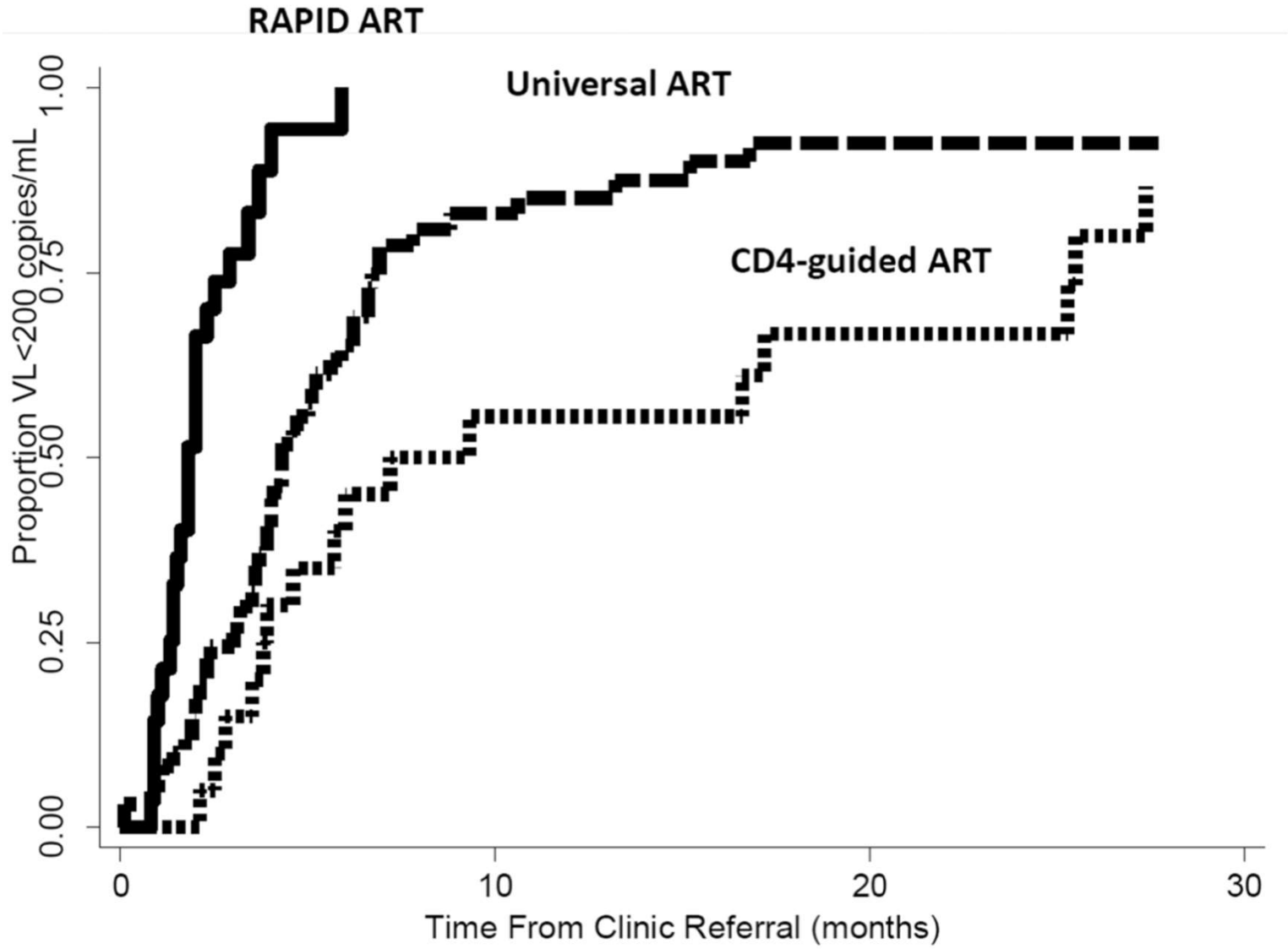
Same-Day Start RCT in Haiti: Results

Retention in Care by Study Group



Koenig, PLoS Med 2017.

San Francisco RAPID ART Pilot



Pilcher, JAIDS 2017.

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San Francisco RAPID ART Follow-Up

- 225 patients referred for RAPID ART from 2013-2017
  - 216 (96%) were started on immediate ART
- Time to suppression
  - 41 days to < 200 copies/uL; 58 days to < 50 copies/uL
- Viral suppression rate
  - 95.8% achieved viral suppression to < 200 copies/uL at 1 year
  - Over the median of 1.09 years f/u (0-3.92 years), 92.1% achieved viral suppression

Coffey, AIDS 2019.

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Summarizing Same-Day ART Start Data

- RapIT RCT in Sub-Saharan Africa[1]
  - Offering single-visit ART initiation to adult patients in South Africa increased uptake of ART by 36% and viral suppression by 26%
- Haiti RCT[2]
  - Same day HIV testing and ART initiation improved retention in care and virologic suppression
  - Qualitative results showed increased hope and connection to care with same-day ART start
- San Francisco RAPID start[3-4]
  - Time to suppression quicker, but it is resource intensive

1-Rosen, PLoS Med 2016. 2-Koenig, PLoS Med 2017. 3-Pilcher, JAIDS 2017. 4-Coffey, AIDS 2019.

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Challenges to Same-Day ART Start

- Barriers cited from Haiti study
  - Wait time in clinic
  - Transportation
  - Costs
- Requires on call clinicians, SW, RNs, pharmacy, counseling
- Insurance coverage
- Resource intensive endeavors

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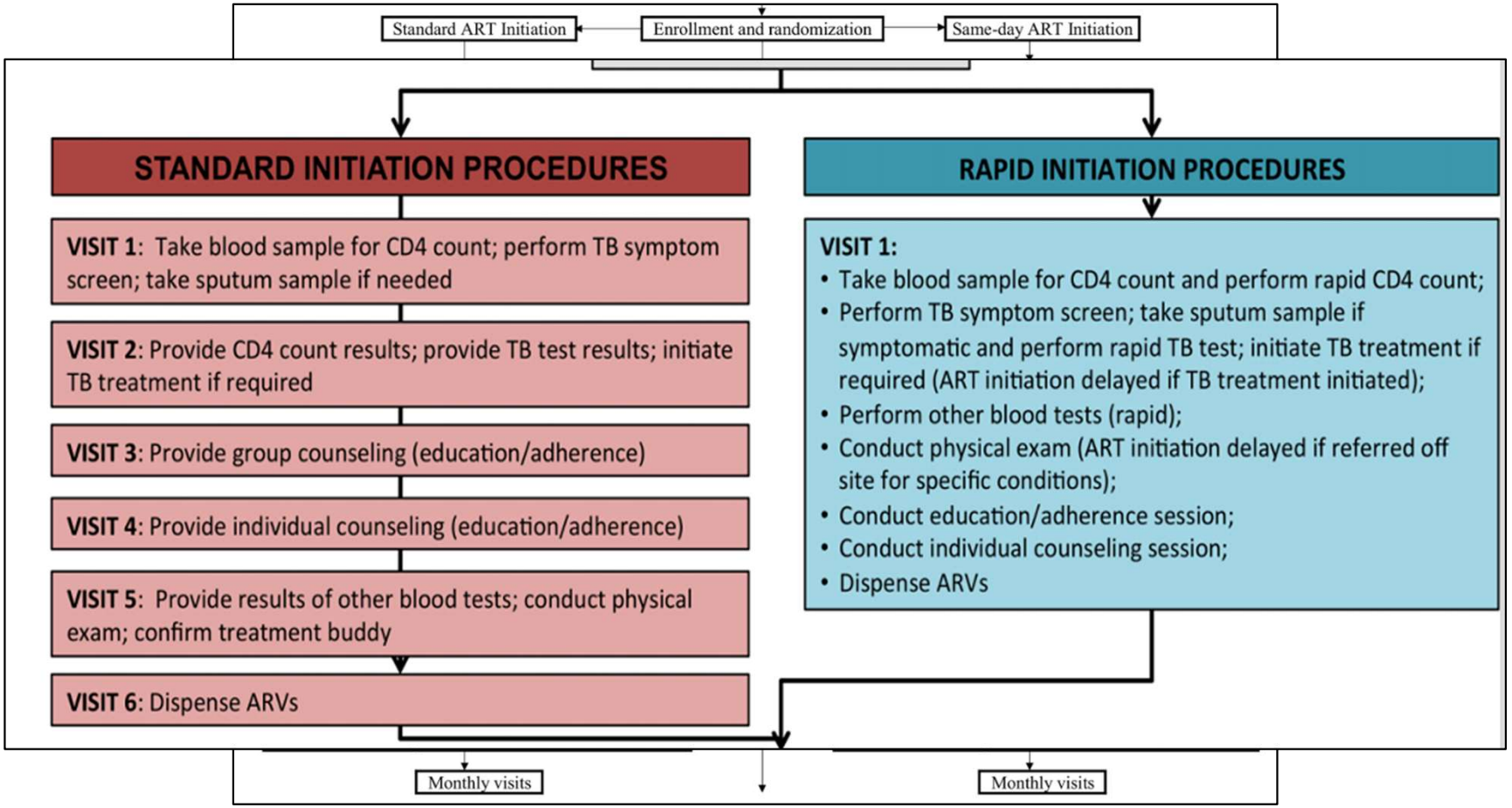
Study Protocols for Same–Day ART Start



Rosen, PLoS Med 2016. Koenig, PLoS Med 2017.

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Same-Day ART Start DHHS Conclusions

- "Whether rapid ART initiation improves long-term care engagement and virologic suppression is not yet known."

- "While the infrastructure and resources necessary to implement an immediate ART program may not be available in all health care settings, removing structural barriers in order to facilitate rapid ART initiation may improve outcomes in the United States."

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Accessed 2/16/2020.

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#3 - Audience Response Question

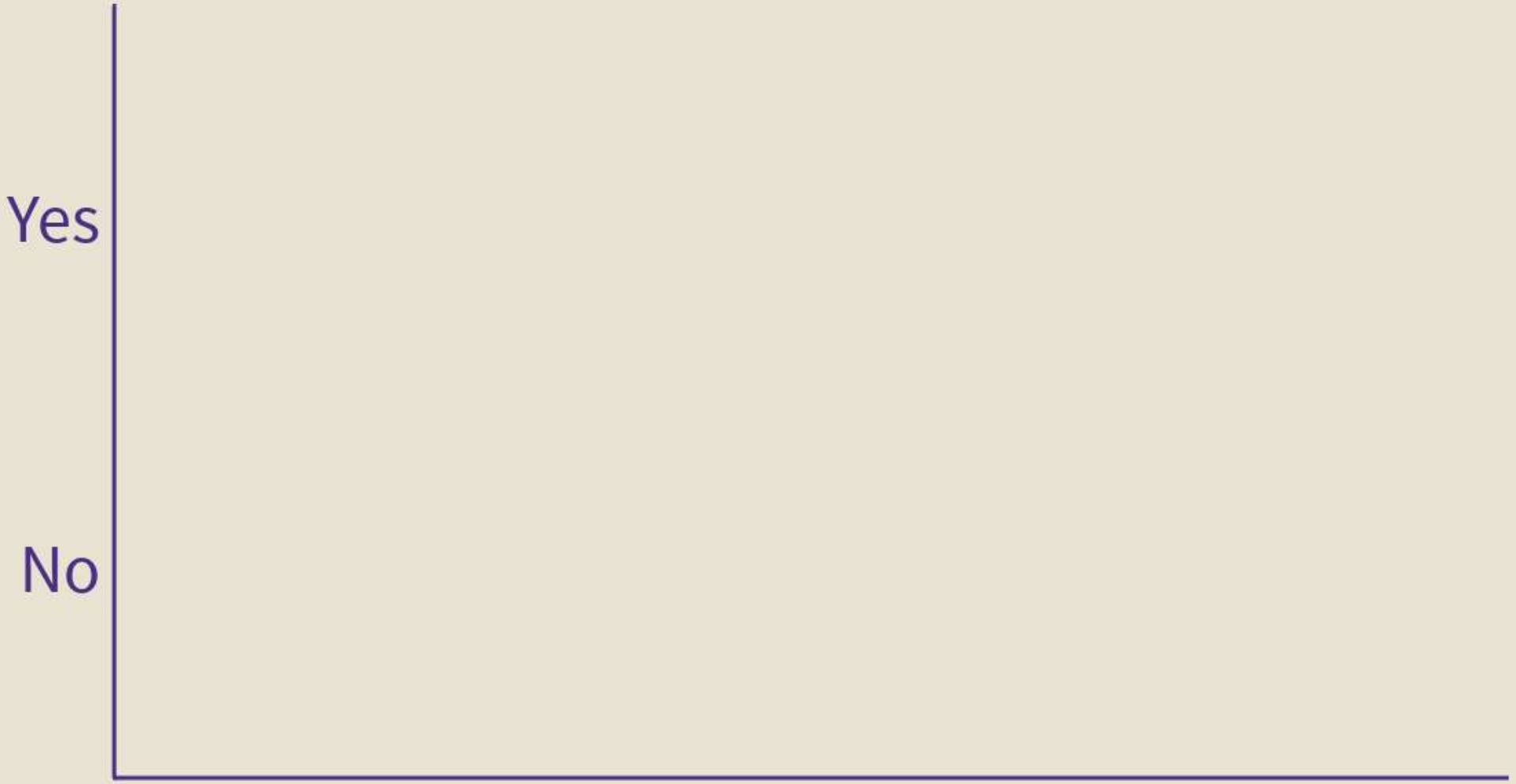
If resources and finances were not an issue, would you do same-day ART start?

A. Yes

B. No

C. Maybe

If resources and finances were not an issue, would you do same-day ART start?



Roadmap

- Transmitted Drug Resistance
- Same-Day ART Start
- ART Options to Start

What to Start in "Most People?"

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- BIC/TAF/FTC **(AI)**
- DTG/ABC/3TC **(AI)—if HLA-B*5701 negative**
- DTG plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
- RAL plus (TAF or TDF)[a] plus (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC)

INSTI plus 1 NRTI:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Accessed 2/16/2020.

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IAS-USA 2018 ART Guidelines

Box 2. Selected Recommendations for Initial ART Regimens[a]

Generally Recommended Initial Regimens (Listed in Alphabetic Order by InSTI Component)

- Bictegravir/TAF/emtricitabine (evidence rating AIa)[b]
- Dolutegravir/abacavir/lamivudine (evidence rating AIa)[c,d]
- Dolutegravir plus TAF/emtricitabine (evidence rating AIa)[c,e]

Saag et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults. 2018 Recommendations of the International Antiviral Society-USA Panel. JAMA. 2018;320(4): 379-396.

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DHHS recommendations if early ART start

Clinical Scenario	Consideration(s)	Rationale/Comments
ARV should be started before HIV drug resistance results are available (e.g., in a person with acute HIV) or when ART is being initiated rapidly.	**Avoid NNRTI-based regimens and DTG/3TC.** **Avoid ABC.** **Recommended ART Regimens:** • BIC/TAF/FTC • DTG plus (TAF or TDF)[a] plus (3TC or FTC) • (DRV/r or DRV/c) plus (TAF or TDF)[a] plus (3TC or FTC)	Transmitted mutations conferring NNRTI and NRTI resistance are more likely than mutations associated with PI or INSTI resistance. HLA-B*5701 results may not be available rapidly. Transmitted resistance to DRV, BIC, and DTG is rare, and these drugs have high barriers to resistance.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Accessed 2/16/2020.

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#4 - Audience Response Question

How do you feel about the updated DHHS guidelines to consider DTG/3TC as an initial regimen for most people?

A. It is about time – I love this!

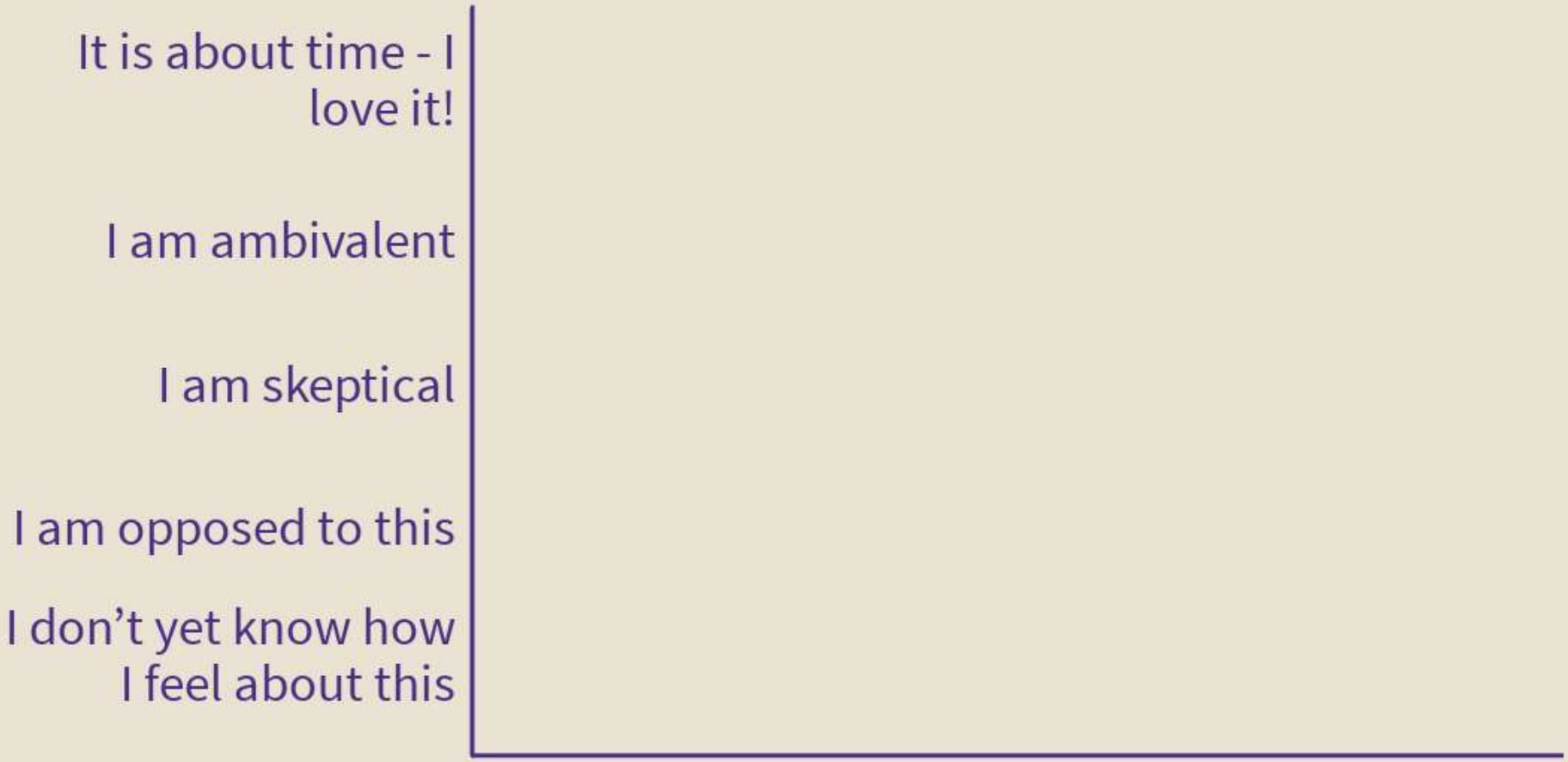
B. I am ambivalent

C. I am skeptical

D. I am opposed to this

E. I don't yet know how I feel about this

How do you feel about the updated DHHS guidelines to consider DTG/3TC as an initial regimen for most people?



GEMINI Background: DTG/3TC vs Triple ART

Study Design: GEMINI 1 and 2

- **Background**:
  - Two identical, double-blind, multinational, noninferiority randomized controlled trials that compared initial antiretroviral therapy (ART) of DTG + 3TC versus DTG + TDF-FTC

- **Enrollment Criteria:**
  - Treatment-naïve adults
  - HIV RNA 1,000-500,000 copies/mL
  - No NRTI, INSTI, or major PI mutations
  - No chronic HBV
  - No need for HCV therapy
  - Not pregnant or breastfeeding

DTG + 3TC
(Dual ART)
n = 716

DTG + TDF-FTC
(Triple ART)
n = 717

Cahn P, et al. Lancet. 2019;393:143-55.

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GEMINI: Baseline Characteristics

GEMINI 1 and 2 Baseline Characteristics		
Characteristic	**DTG + 3TC** (n = 716)	**DTG + TDF-FTC** (n = 717)
Age, years, median (IQR)	32 (26-40)	33 (26-42)
Female, n (%)	113 (16)	98 (14)
White, n (%)	480 (67)	497 (69)
Black or African American, n (%)	99 (14)	76 (11)
CD4 cell count, mean (SD)	462 (219.2)	461.3 (213.1)
CD4 count ≤200 cells/mm^3, n (%)	63 (9)	55 (8)
HIV RNA ($\log_{10}$ copies/mL)	4.42 (0.66)	4.45 (0.65)
≤100,000 copies/mL, n (%)	576 (80)	564(79)
>100,000 copies/mL, n (%)	140 (20)	153 (21)

Source: Cahn P, et al. Lancet. 2019;393:143-55.

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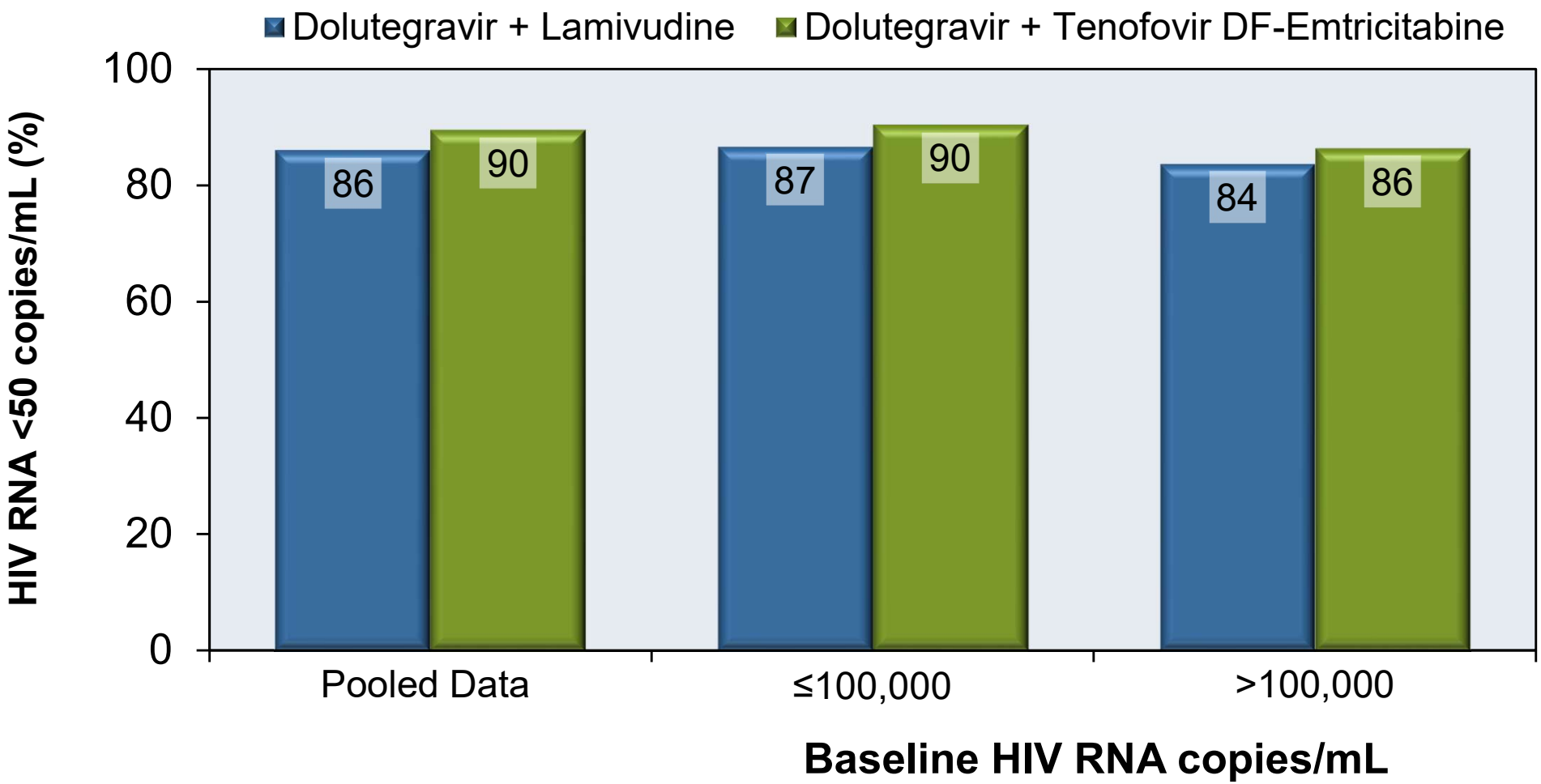
GEMINI Week 96 Results by Baseline HIV RNA Level



Cahn P, et al. J Acquir Immune Defic Syndrome. 2019 Dec 10. Epub ahead of print

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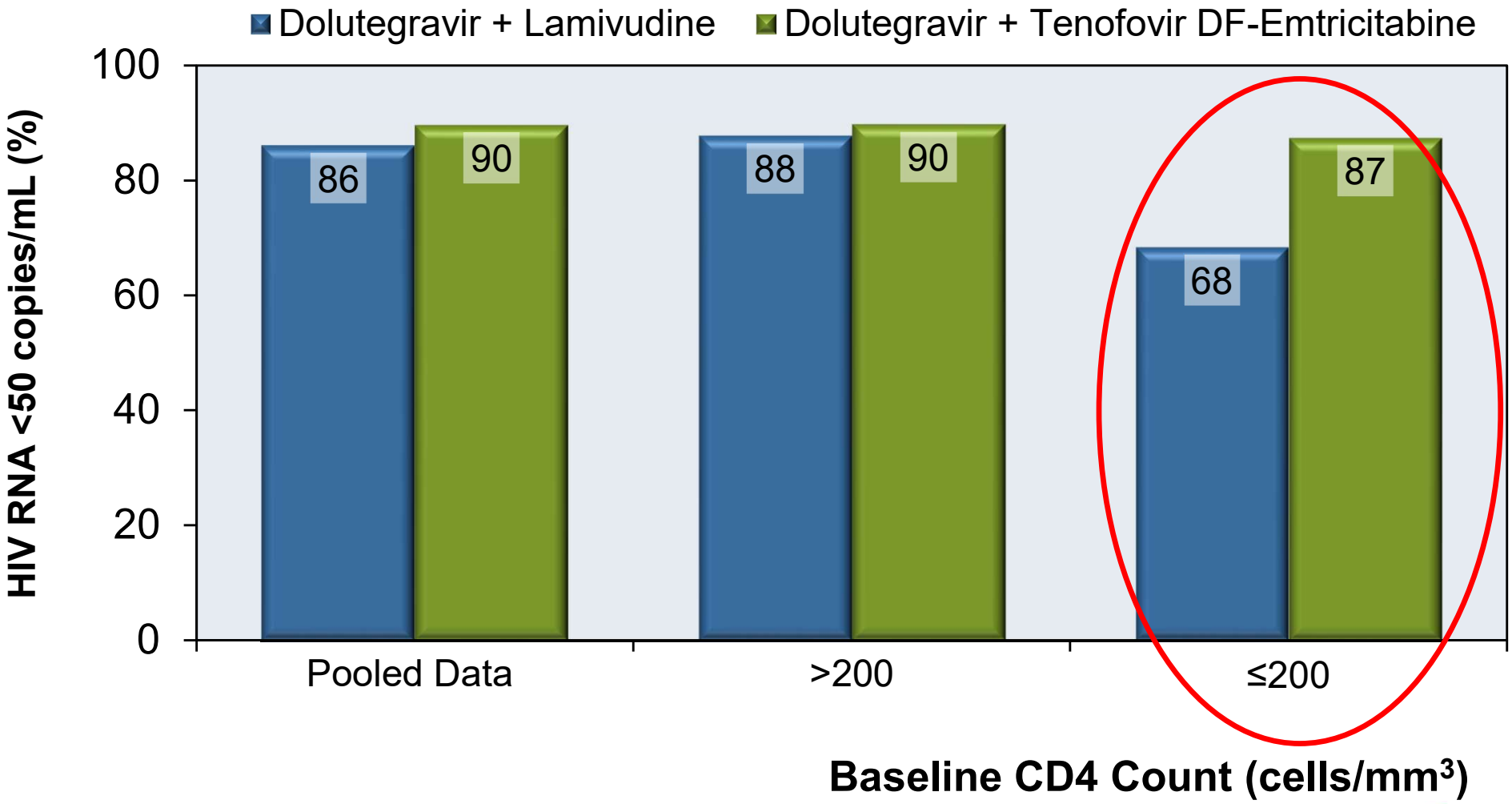
GEMINI Week 96 Results by Baseline CD4 Cell Count



Cahn P, et al. J Acquir Immune Defic Syndrome. 2019 Dec 10. Epub ahead of print

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What about DTG/3TC in the real world?

- VACH Clinical Cohort
  - Retrospective, clinic-based cohort study in Spain 2016-2019
  - 617 people switched to DTG arm & 5047 to triple therapy
    - DTG arm: 2/3 on DTG/RPV, 1/3 DTG/3TC
    - Triple therapy arm: Most on DTG/3TC/ABC or EVG/c/TAF/FTC
  - Endpoints:
    1. Time to discontinuation due to failure
    2. Risk of discontinuation due to failure
    3. Time to discontinuation due to adverse events
    4. Risk of adverse events

Tiera R et al. EACS 2019 PS8/5

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VACH Clinical Cohort: Baseline Characteristics

	INSTI-based Triple Therapy	DTG+3TC or DTG+RPV
Age (years), Mean (SD)	48.1 (10.7)	52.0 (10.3)
Gender, % Female	23.4	28.7
AIDS diagnosis, % yes	23.2	26.7
CD4 count, % > 350 cells/mm^3	81.8	82.9
Viral load, % <50 copies/mL	81	90.2
Duration of ART regimens (years), mean (SD)	12.0 (8.4)	14.9 (8.1)
# of previous ART regimens, Mean (SD)	5.3 (3.6)	7.4 (4.6)
# of previous virologic failures, Mean (SD)	1.1 (2.4)	1.5 (2.9)
HCV, % yes	32.6	35.4

Slide adapted from Dhanireddy S. Teira R, EACS 2019 PS8/5

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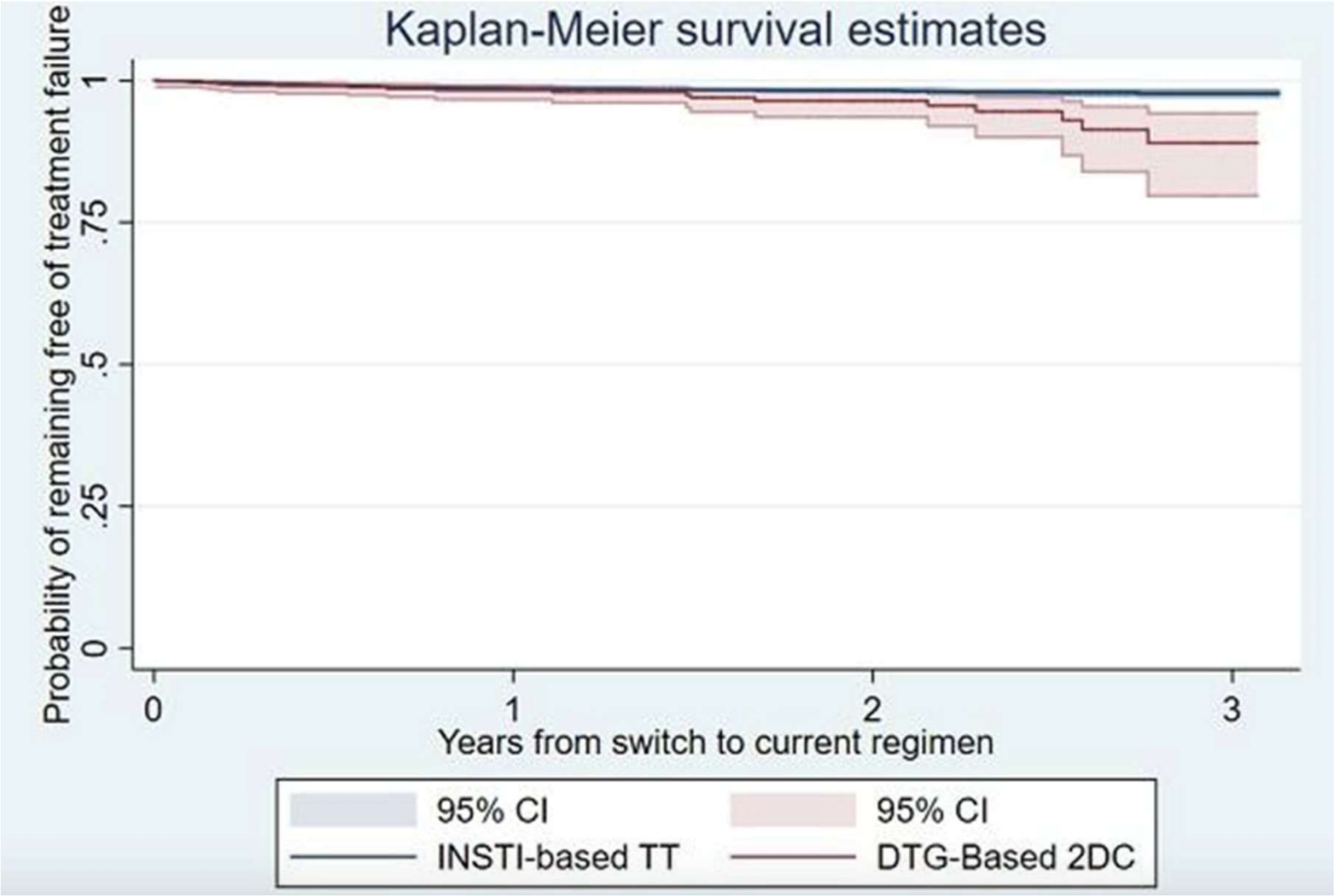
VACH Clinical Cohort: Results



Teira R, EACS 2019 PS8/5

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VACH Clinical Cohort: Summary

- They found that PWH switching to a two-drug regimen (DTG/RPV or DTG/3TC) **had more than a doubled risk of discontinuation** due to treatment failure (adjusted hazard ratio [aHR] 2.3, 95% confidence interval [CI] 1.3 to 4.1, P = 0.003)

- No difference between the regimens in discontinuation for adverse events

- There was more treatment failure in those switched to DTG/RPV or DTG/3TC as compared to INSTI-based triple therapy

Tiera R et al. EACS 2019 PS8/5

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#5- Audience Response Question

Now, how do you feel about considering DTG/3TC as an initial regimen for most people?

A. It is great!

B. I am ambivalent

C. I am skeptical

D. I am opposed to this

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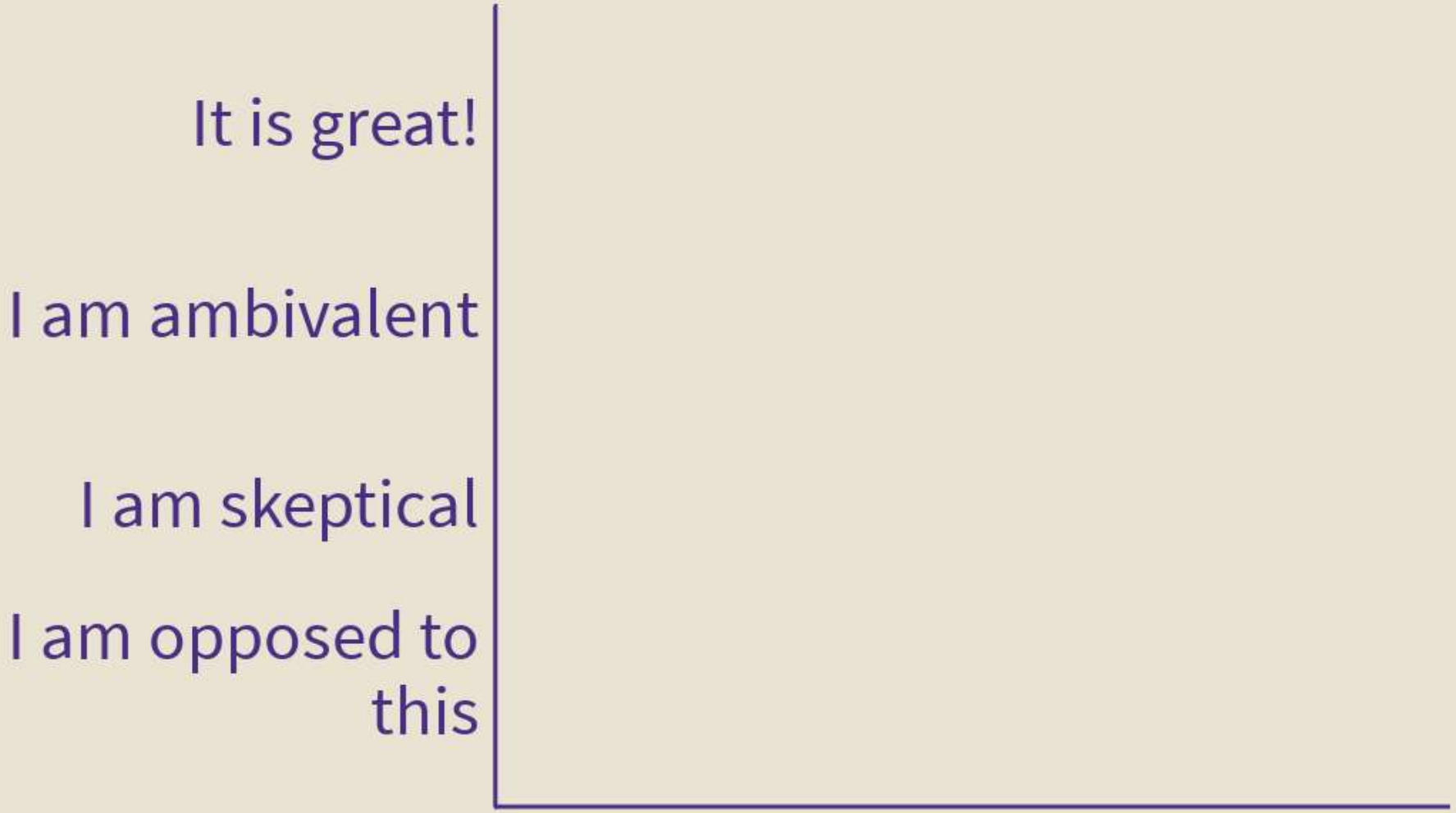
Now, how do you feel about considering DTG/3TC as an initial regimen for most people?



Conclusions

- Rates of INSTI TDR are low. How does this affect your practice of checking baseline genotypes?

- Same-day ART start is aspirational, but resource intensive. We need more data in the US and to answer whether it affects virologic suppression in the long term.

- If you are going to start DTG/3TC, be aware of the inclusion criteria from the GEMINI study and consider real-world effects. Beware DTG/3TC use in those with CD4 < 200 cells/mm^3.

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