

# Genotypic Resistance Testing in Routine Care in South Africa:

## Is the Juice Worth the Squeeze?

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# Conflicts of Interest<sup>^\*</sup>

- No financial conflicts to report

<sup>^</sup>I am personally conflicted by my own argument

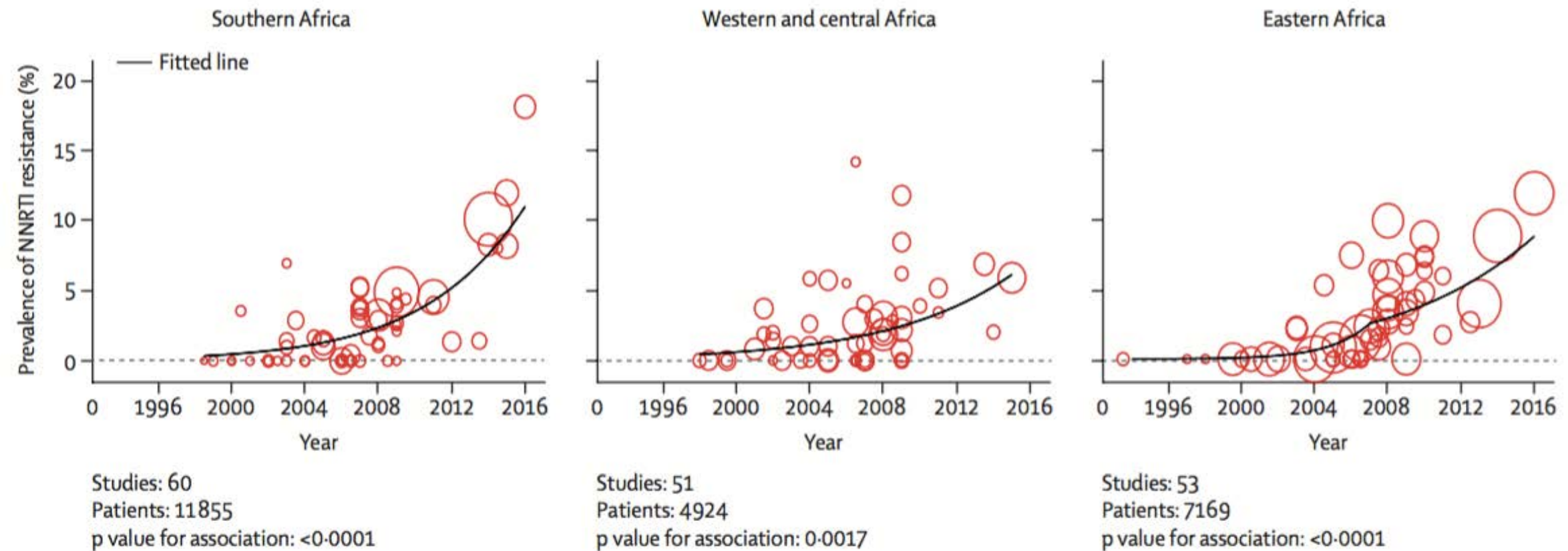
<sup>\*</sup>Also I am not a modeler so I hope you did not come to this talk to see someone give you a convincingly derived, data-driven answer

# The Case Against HIV GRT in SSA

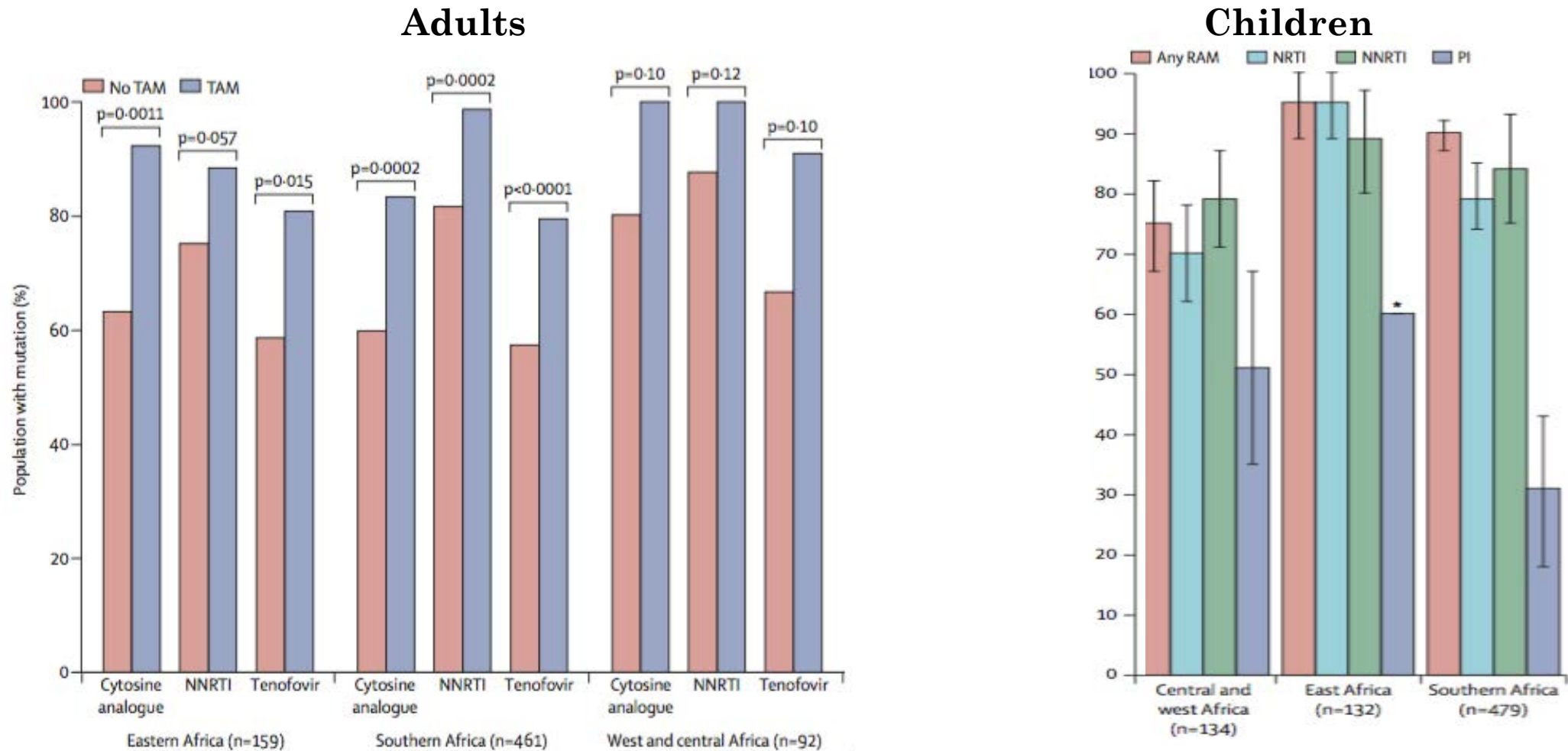
- Resistance is not such a big deal
  - If it is now, it won't be in the era of DTG
- Resistance testing is too expensive
- Resistance testing will not change outcomes

# Resistance is Not Such a Big Deal

# Not such a big deal: TDR

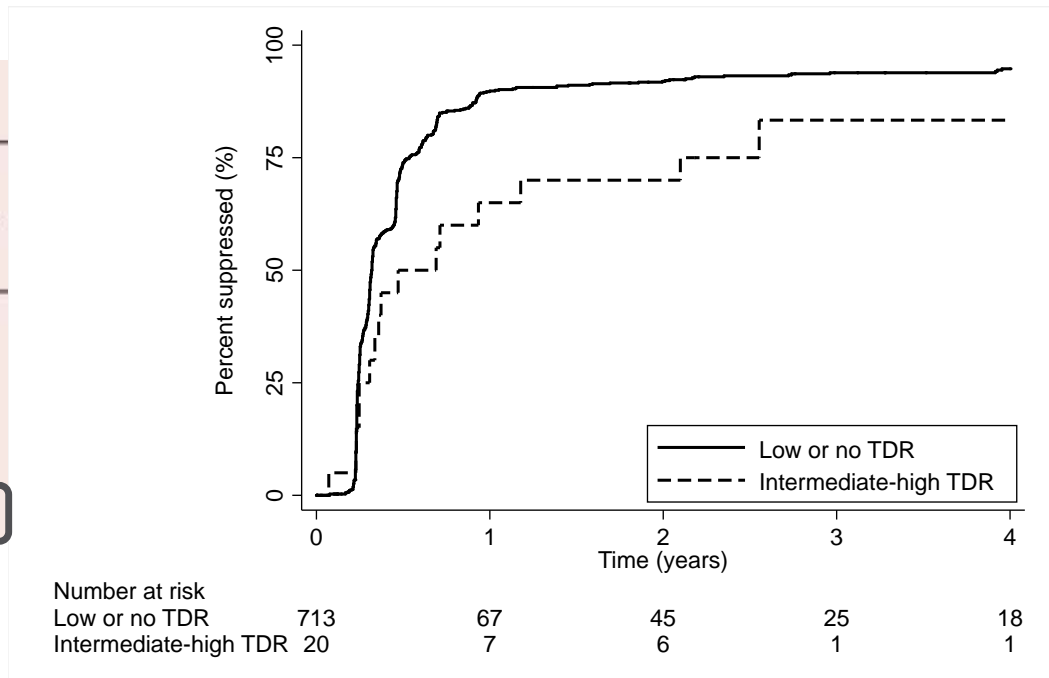


# Not such a big deal: Resistance @ Failure

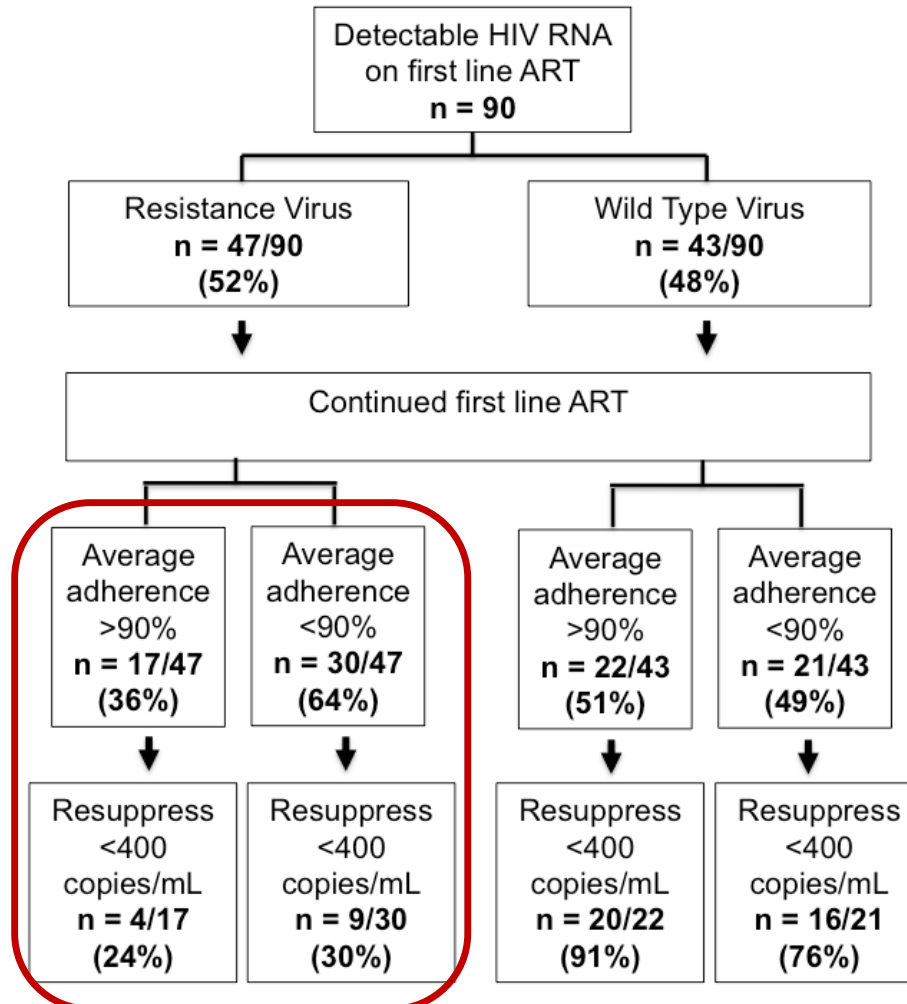


# Not such a big deal: Resistance and outcomes

	Number of events	Multivariate		
		Baseline model		
		OR	95% CI	p value
PDR				
No PDR	174	1	..	..
PDR and fully active ART	6	1.01	0.55-1.87	0.964
PDR and partly active ART	21	2.13	1.44-3.14	<0.0001

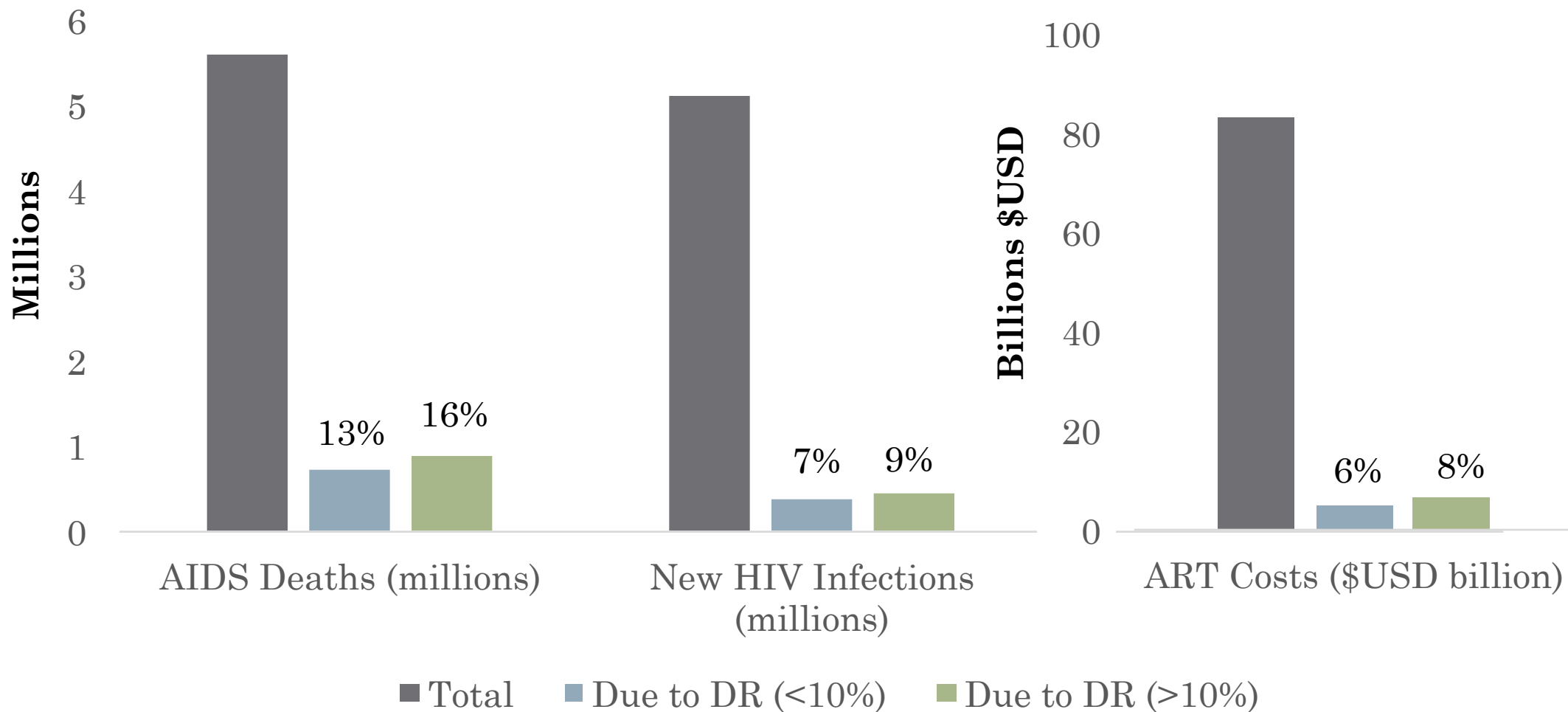


# Not such a big deal: Resistance and outcomes





# Not such a big deal: Deaths and costs



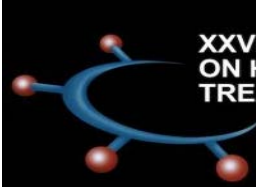
# Will DTG Save Us from Resistance?

	SPRING-2 <sup>1</sup> (to Week 96)*		SINGLE <sup>2</sup> (to Week 144)*		FLAMINGO <sup>3</sup> (to Week 96) <sup>†</sup>		ARIA <sup>4</sup> (to Week 48) <sup>‡</sup>	
	DTG + 2NRTI (n=411)	RAL + 2NRTI (n=411)	DTG + ABC/3TC (n=414)	EFV/ TDF/FTC (n=419)	DTG + 2NRTI (n=242)	DRV/r + 2NRTI (n=242)	DTG/ABC/3TC (n=248)	ATV/r + TDF/FTC (n=247)
Subjects with persistent virologic failure, n (%)	20 (5)	28 (7)	39 (9)	33 (8)	2 (<1)	4 (2)	6 (2)	4 (2)
Genotypic results at time of failure, n (%)	8	18	–	–	–	–	–	–
<b>INSTI-resistant mutations, n (%)*</b>	<b>0 (0)</b>	1 (6)	<b>0 (0)</b>	0 (0)	–	–	<b>0 (0)</b>	0 (0)
RT genotypic results available at time of PDVF, n	12	19	–	–	–	–	–	–
<b>NRTI-resistant mutations, n (%)*</b>	<b>0 (0)</b>	4 (21)	<b>0</b>	1 ( K65K/R)	<b>0 (0)</b>	0 (0)	<b>0 (0)</b>	<b>1</b> (M184V)
NNRTI-resistant mutations, n (%)*	–	–	0	6 (K101E, K103N, K103K/N, G190G/A)	0 (0)	0 (0)	–	–
PI-resistant mutations, n (%)	–	–	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

# Can DTG Save Us from Resistance?

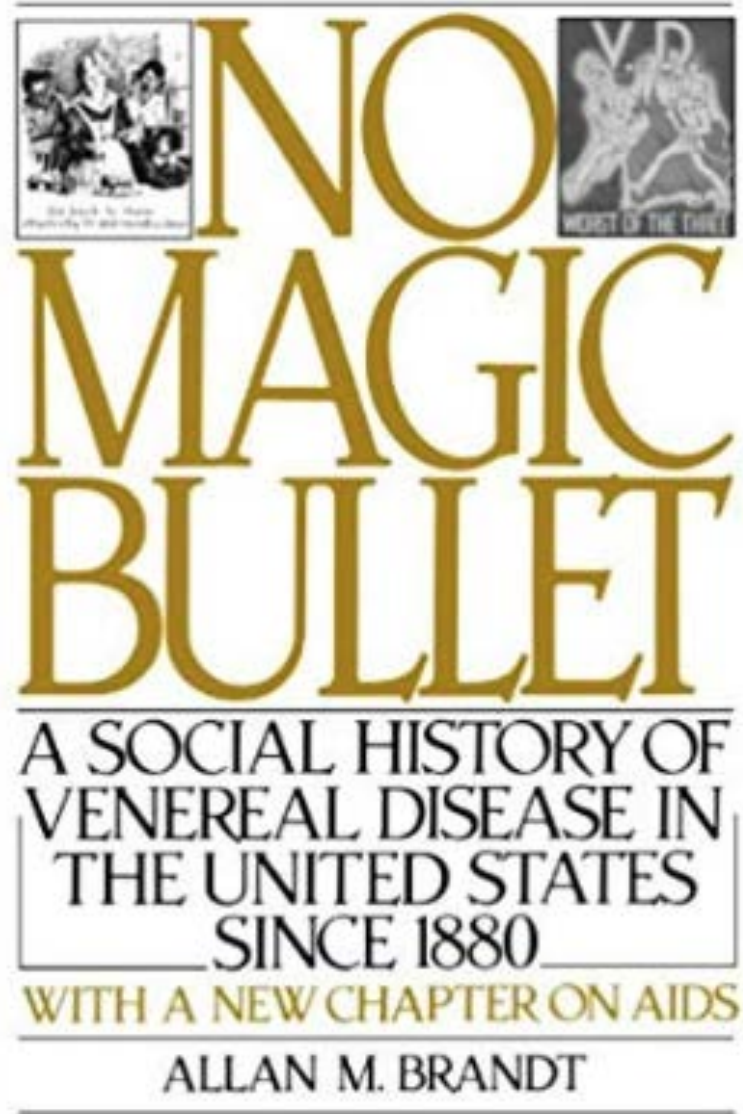
Resistance analysis	DTG + 2 NRTIs (n=8)	LPV/RTV + 2 NRTIs (n=24)
<b>INSTI</b>	<b>0</b>	<b>0</b>
<b>NRTI</b>	<b>0</b>	<b>3*</b>
K70R	0	2
M184V	0	1
K219Q	0	1
K219E	0	1
<b>PI</b>	<b>0</b>	<b>0</b>

- No subject receiving DTG + 2 NRTIs developed INSTI or NRTI resistance-associated mutations.

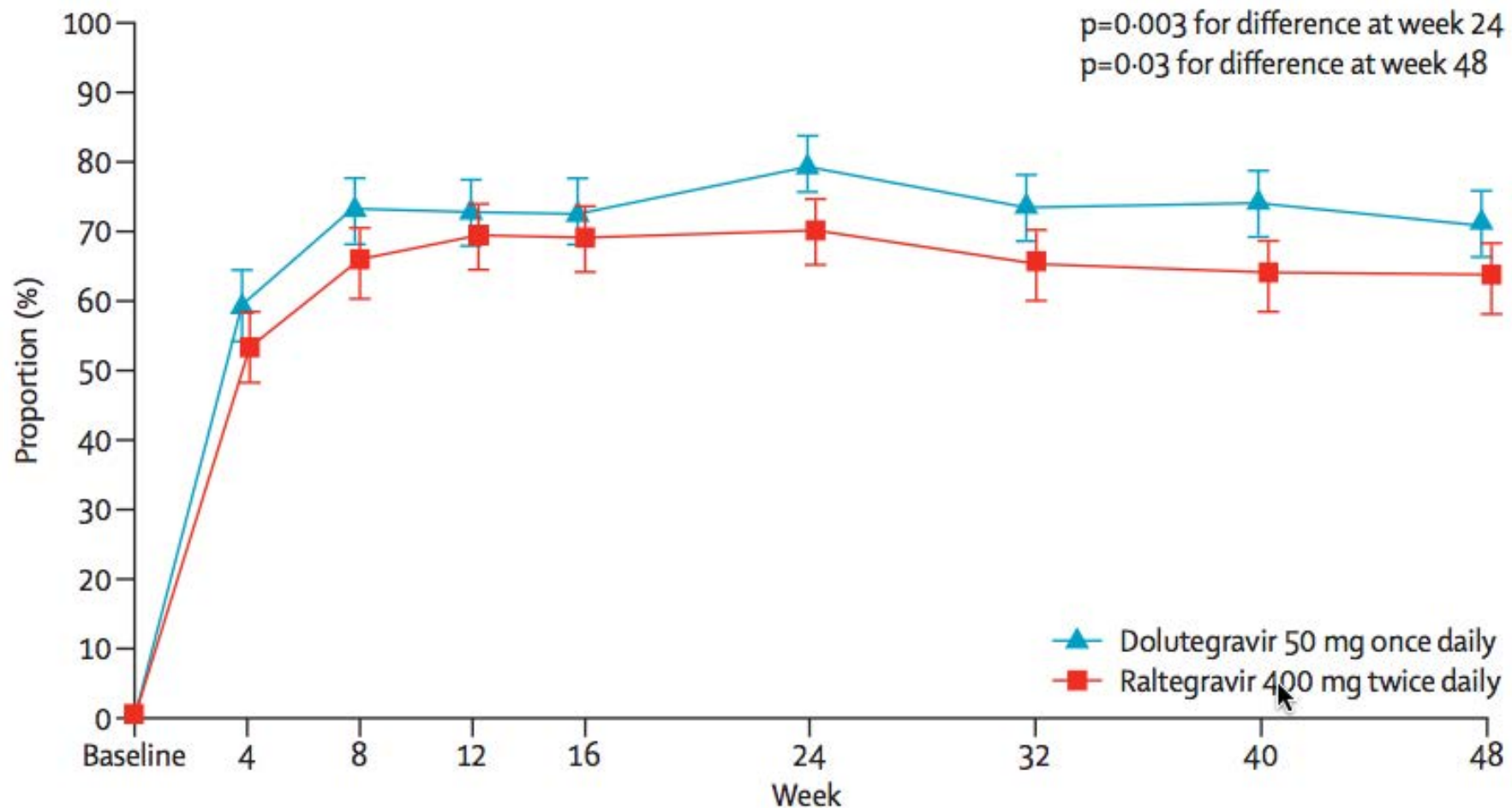


XXVII INTERNATIONAL WORKSHOP  
ON HIV DRUG RESISTANCE AND  
TREATMENT STRATEGIES

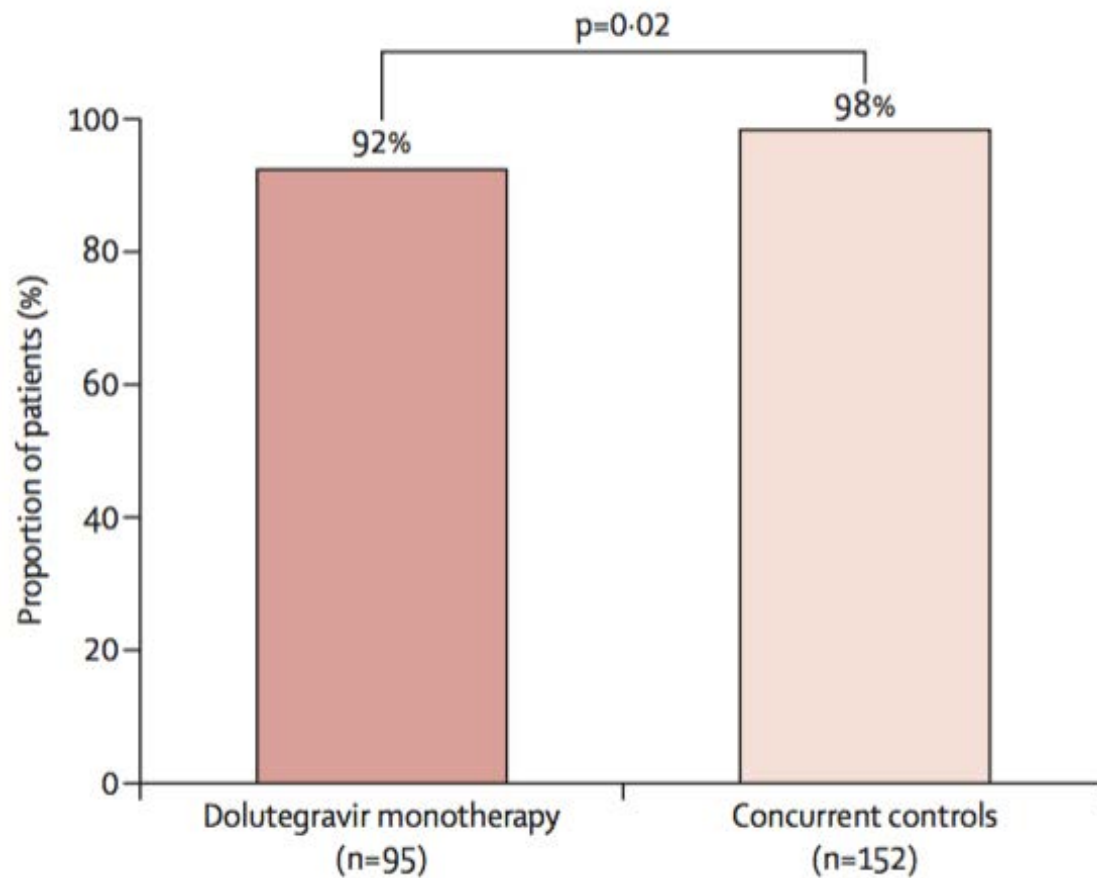
22 - 23 October 2018 Johannesburg, South Africa



# Can DTG Save Us from Resistance?



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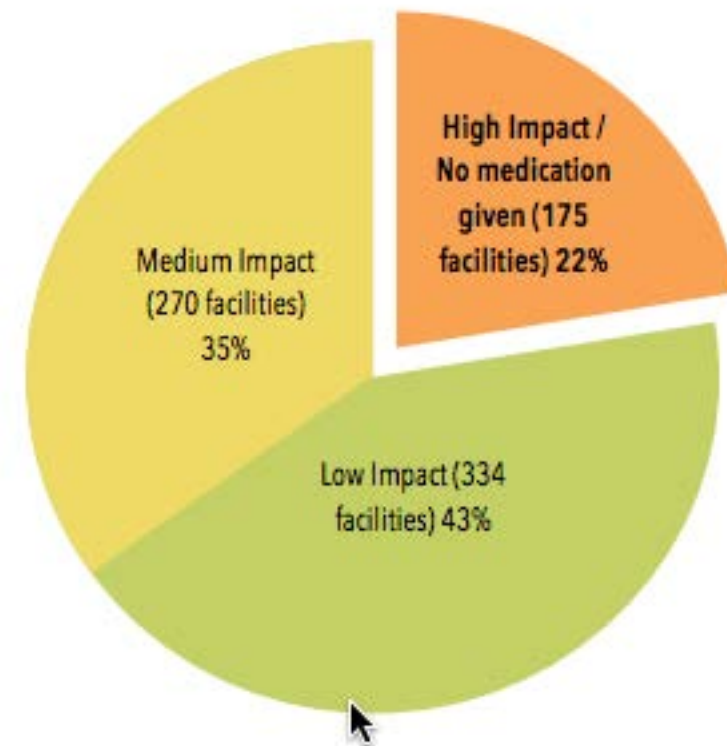
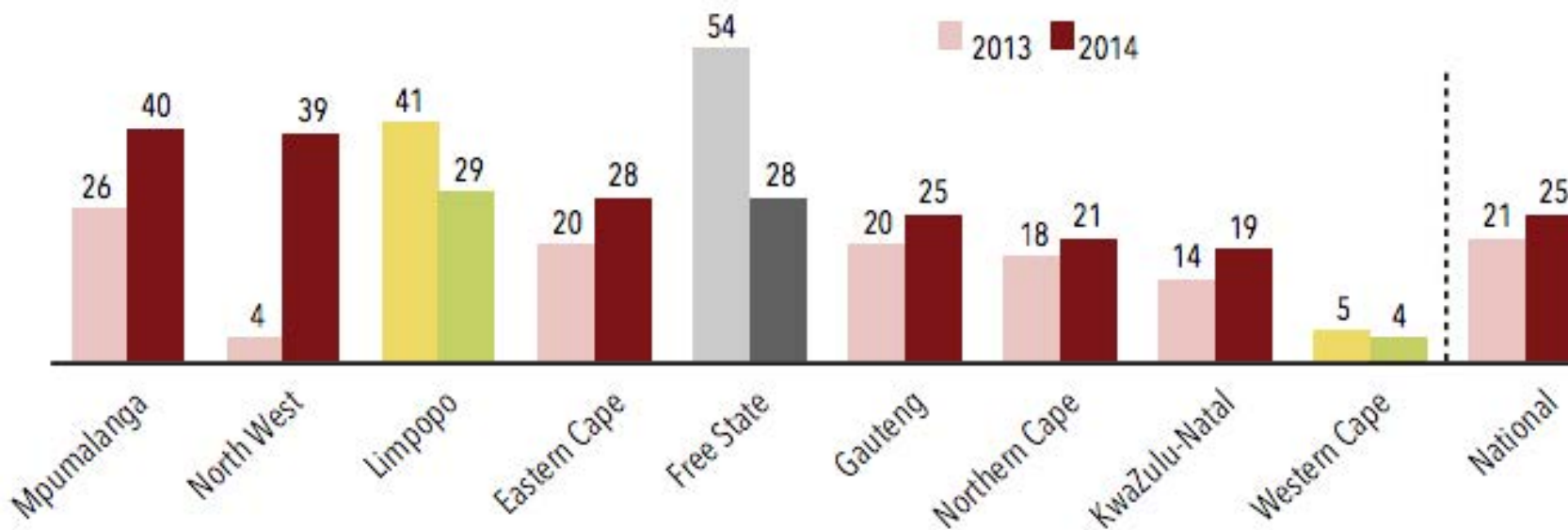
## *Functional* monotherapy in SSA?

- ~60% K65 + M184V at failure
- >70% using NGS



# Can DTG Save Us from Resistance?

## *ACTUAL* monotherapy in SSA



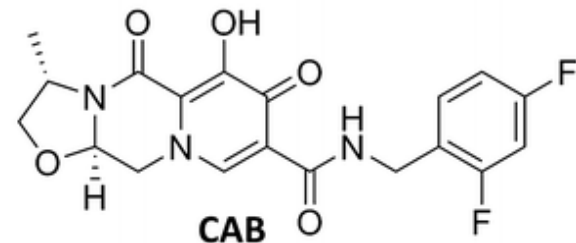
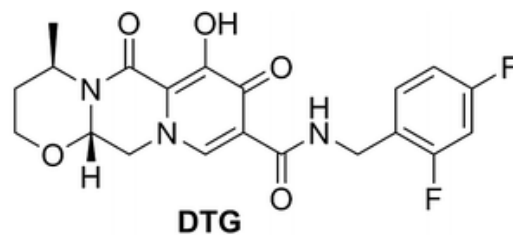
**Proportion of Facilities with at Least one HIV or TB Therapy Stockout**

# Can DTG Save Us from Resistance?

- Who's line is it anyway?

Population	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (including women and adolescent girls who are of childbearing potential or are pregnant) <sup>a</sup>	Two NRTIs + DTG <sup>b</sup>	Two NRTIs + (ATV/r or lopinavir/ritonavir (LPV/r))	Darunavir/ritonavir (DRV/r) <sup>g,h</sup> + DTG <sup>i</sup> + 1–2 NRTIs (if possible, consider optimization using genotyping)
	Two NRTIs + EFV <sup>c</sup>	Two NRTIs + DTG <sup>b</sup>	
Children	Two NRTIs + DTG	Two NRTIs + (ATV/r <sup>d</sup> or LPV/r)	
	Two NRTIs + LPV/r	Two NRTIs + DTG <sup>e</sup>	
	Two NRTIs + NNRTI	Two NRTIs + DTG <sup>f</sup>	

- Cabotegravir as a PrEP & DTG as ART?

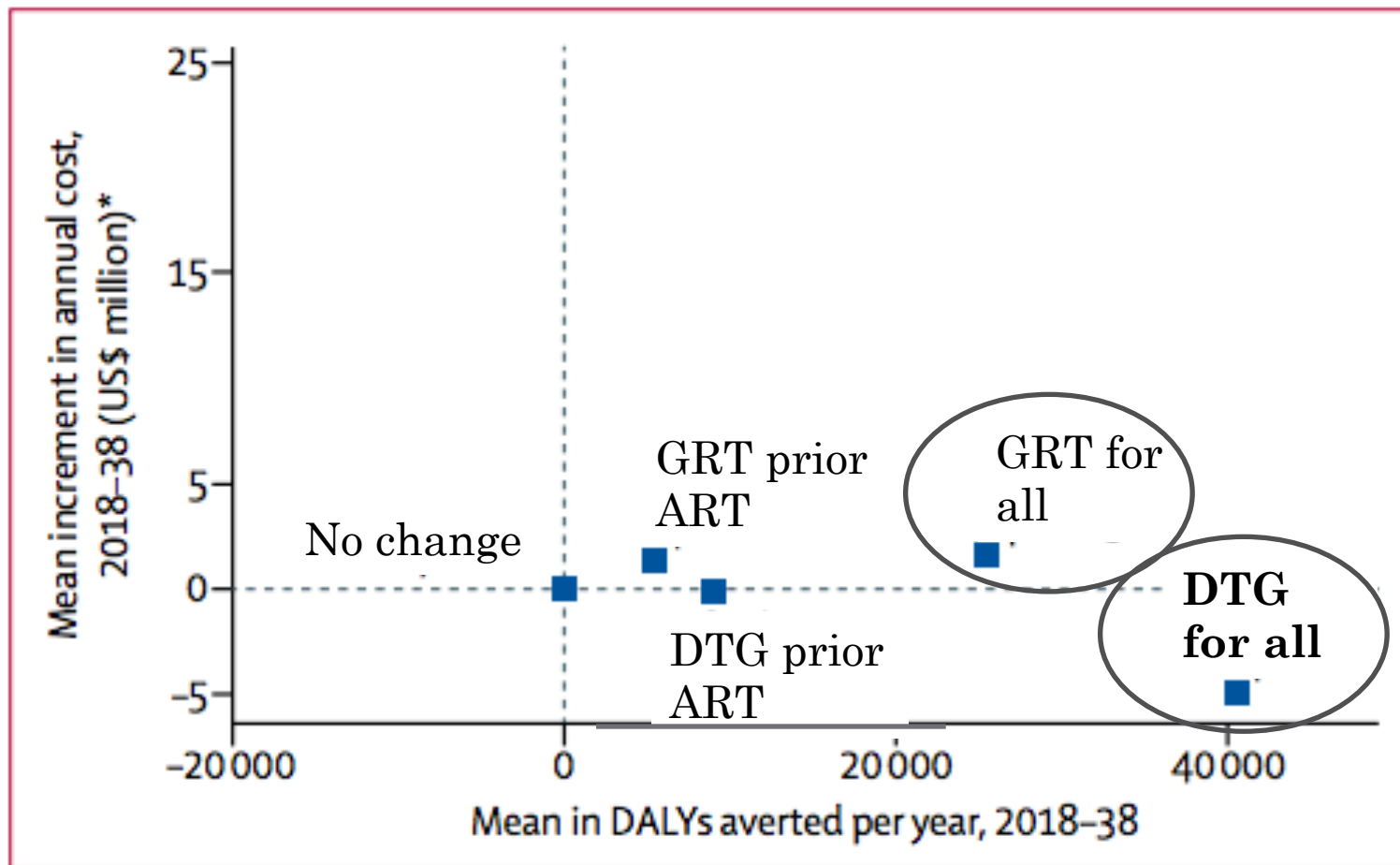


# Resistance Testing is Too Expensive

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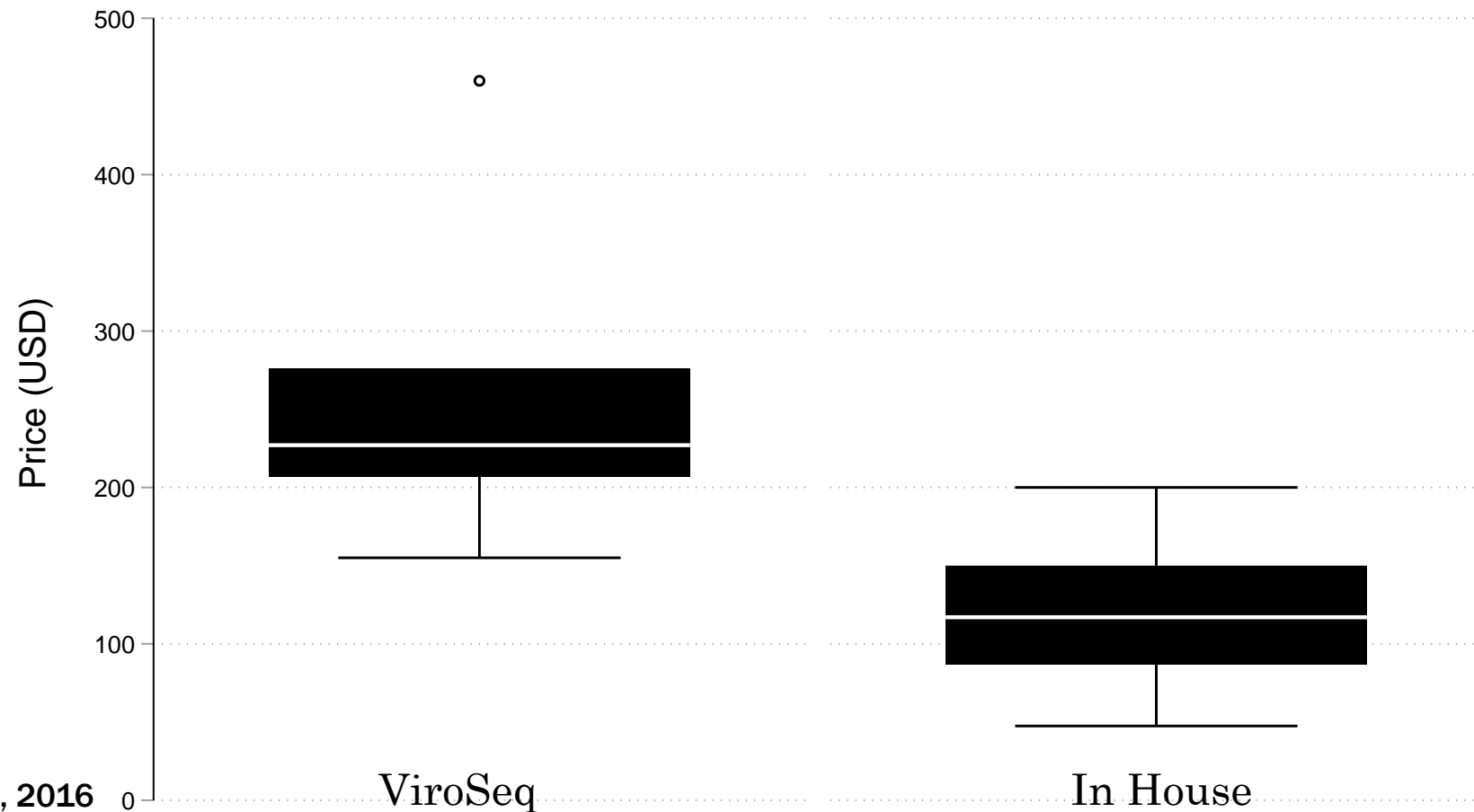
Analysis Model	Population	Perspective	Time Horizon	Outcome	Sensitivity Analysis	Primary Result
Cost-Effectiveness of Preventing AIDS Complications state-transition model [24]	South Africa	Modified societal	Lifetime	Cost/year of life saved	Univariate and multiway	<b>Very cost effective</b>
Cost minimization model [25]	South Africa	Presumed Payer	5 years	Cost per strategy	Deterministic/ Probabilistic	<b>Cost Neutral</b>
HIV synthesis transmission individual-based stochastic model [26]	Zimbabwe	Unstated	10 years	Cost/ disability adjusted life year (DALY) averted	Several one way sensitivity analyses	<b>Not cost-effective</b>

# Cost-Effectiveness of Dolutegravir



# Too expensive: In-house technology

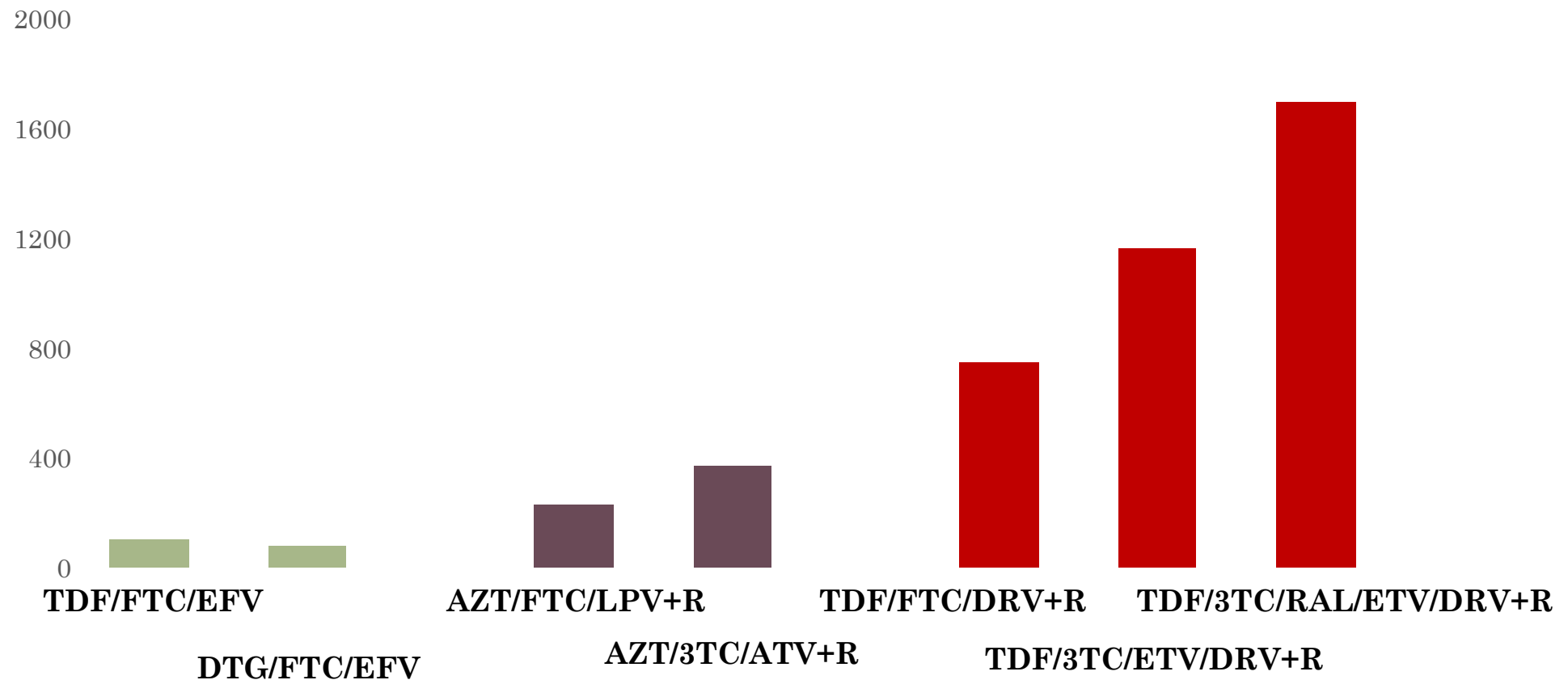
Genotypic Resistance Testing Costs in sub-Saharan Africa



# Too expensive: Limited formulary

	South Africa	United States
NRTIs	<p>Tenofovir disproxil fumarate/FTC  <b>Zidovudine/3TC</b>  <b>Abacavir/3TC</b></p>	<p>Tenofovir alafenamide fumarate/FTC  Tenofovir disproxil fumarate/FTC  Abacavir/3TC</p>
NNRTIs	<p>Efavirenz</p>	<p><b>Rilpivirine</b>  <b>Doravirine</b>  <b>Efavirenz</b>  <b>Etravirine</b></p>
INSTIs	<p>Dolutegravir (any day/month now...)  Raltegravir (highly restricted)</p>	<p>Dolutegravir  Bictegravir  Elvitegravir  Raltegravir</p>
PIs	<p><b>Lopinavir/ritonavir</b>  Atazanavir/ritonavir (restricted)  Darunavir/ritonavir (highly restricted)</p>	<p><b>Darunavir/ritonavir</b>  <b>Atazanavir/ritonavir</b></p>
Others		<p><b>Maravacoc</b>  Ibalizumab</p>

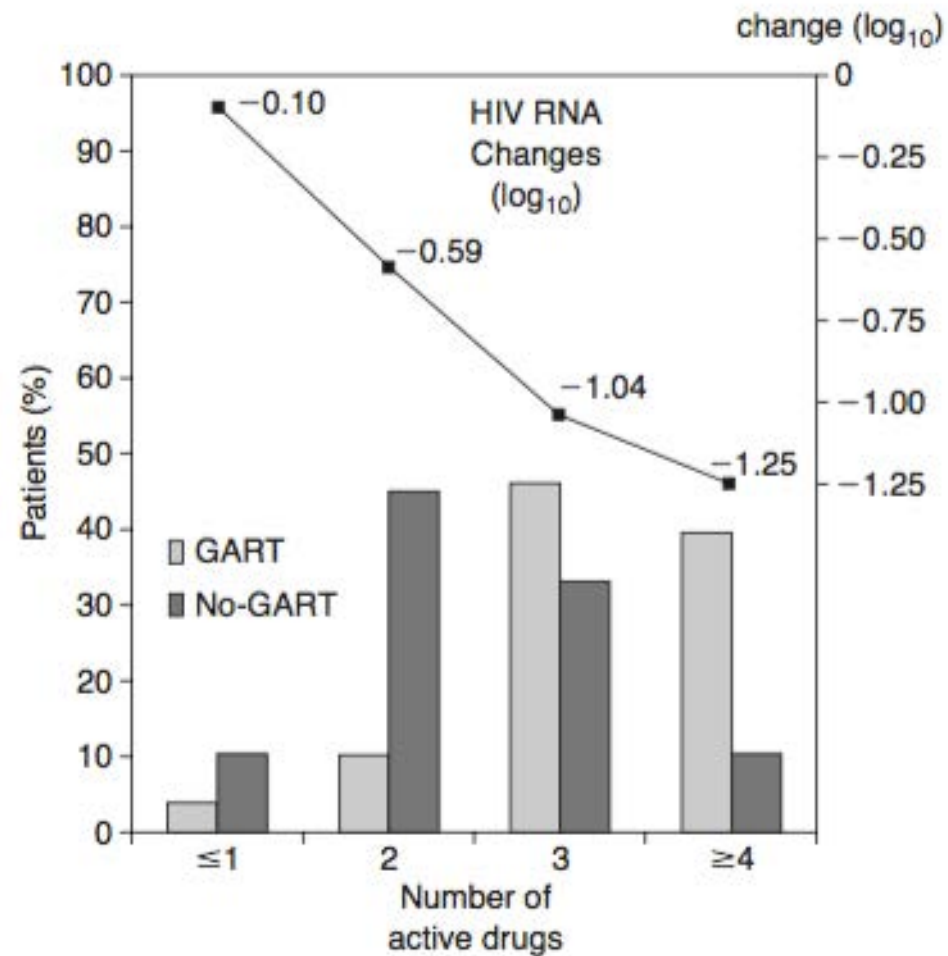
# Too expensive: Cost of not testing?



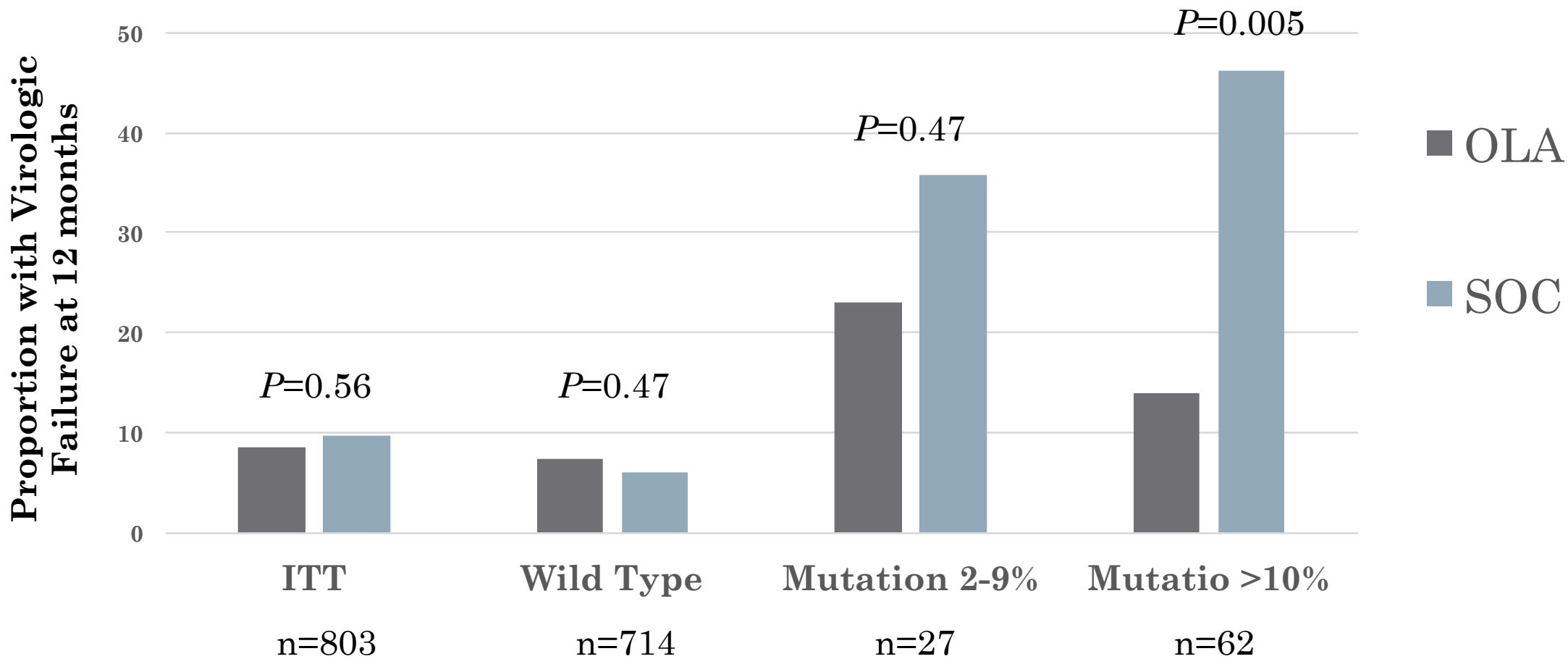


# Resistance Testing Doesn't Improve Outcomes

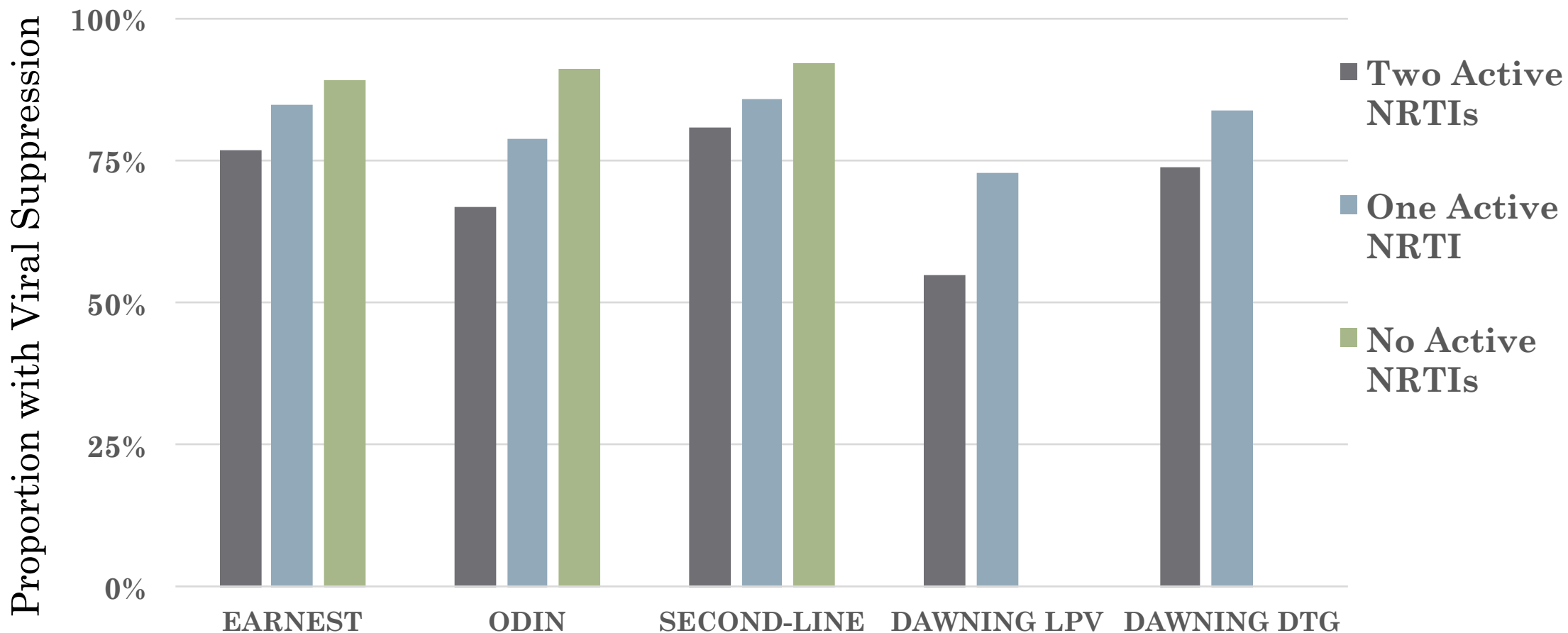
# Resistance Testing Doesn't Improve Outcomes



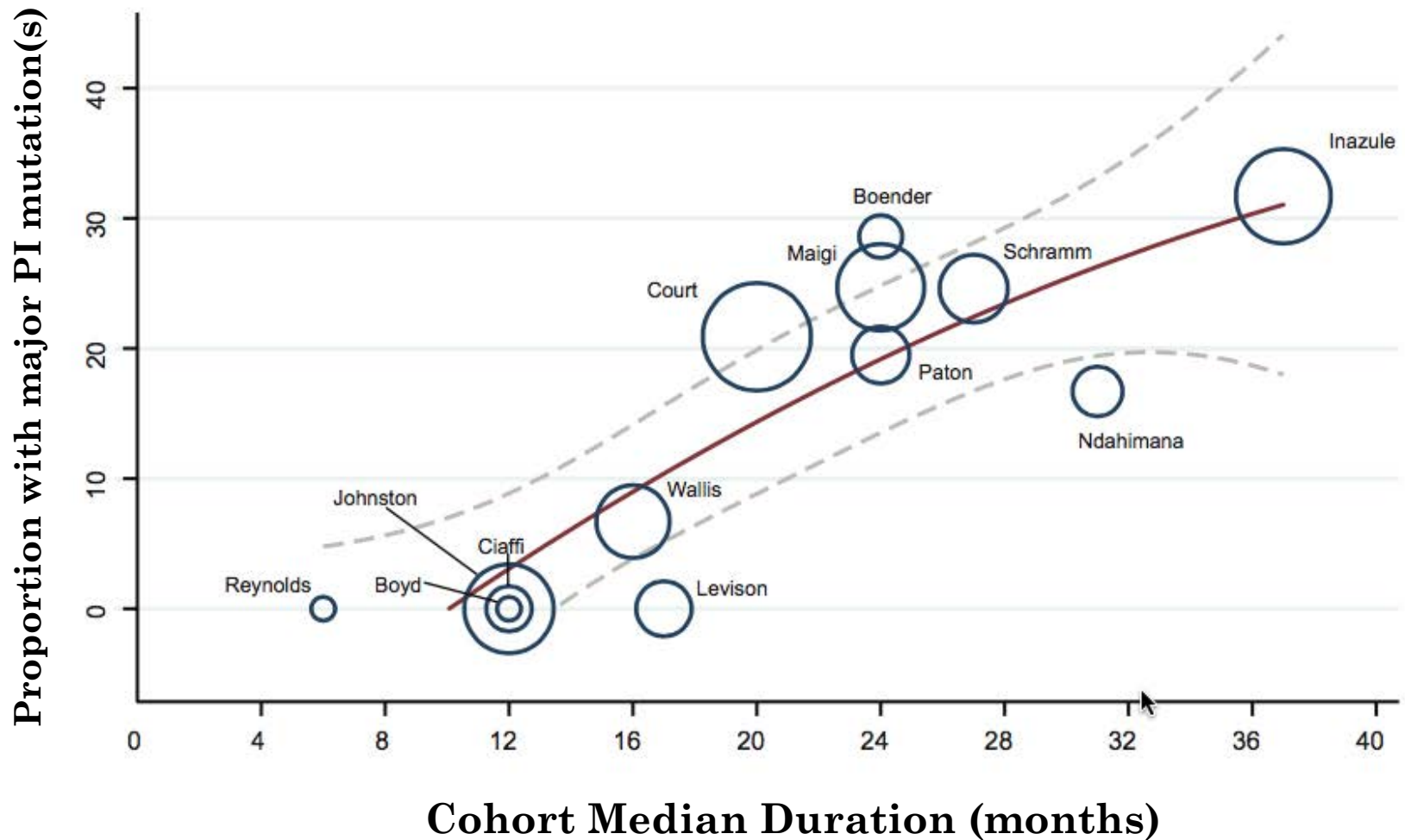
# Resistance Testing Doesn't Improve Outcomes



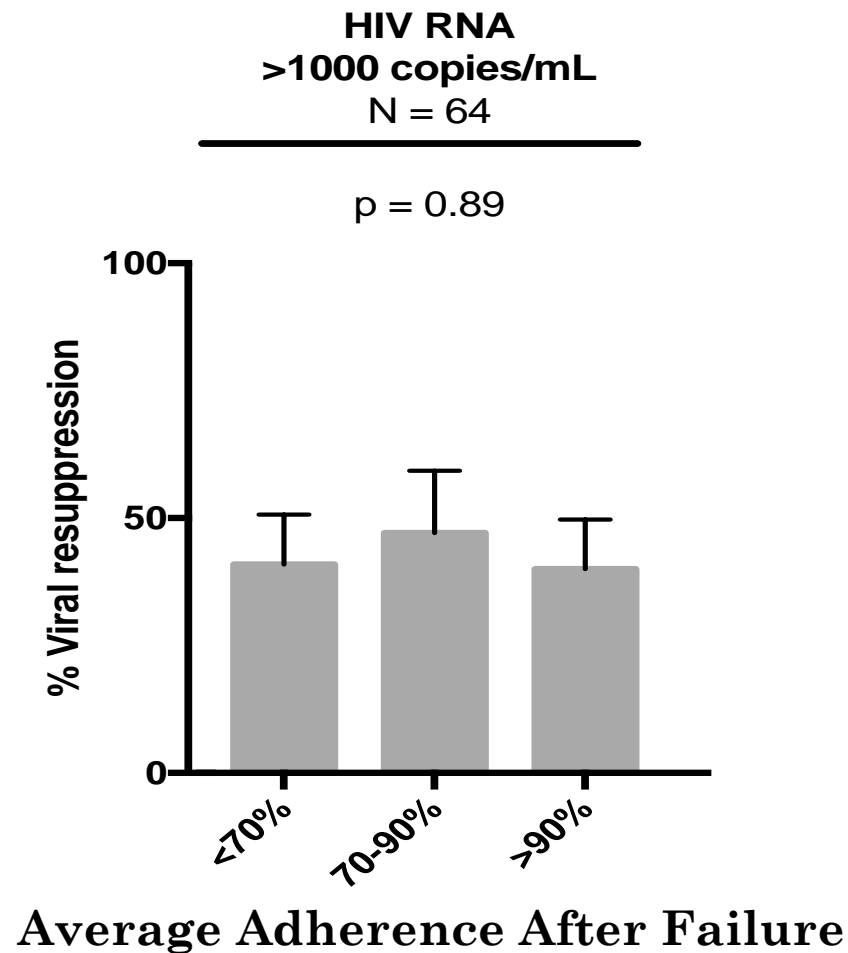
# Resistance Testing Doesn't Improve Outcomes



# Resistance Testing Doesn't Improve Outcomes



# Resistance Testing Doesn't Improve Outcomes



# Resistance Testing Will Not Change Outcomes

- Can a resistance test be an adherence intervention for patients?

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## Resistance Testing to Improve Management of Virologic Failure in Sub-Saharan Africa (REVAMP)



National Institute of  
Allergy and  
Infectious Diseases



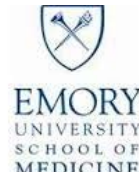
ClinicalTrials.gov Identifier: NCT02787499

Recruitment Status ⓘ: Recruiting

First Posted ⓘ: June 1, 2016

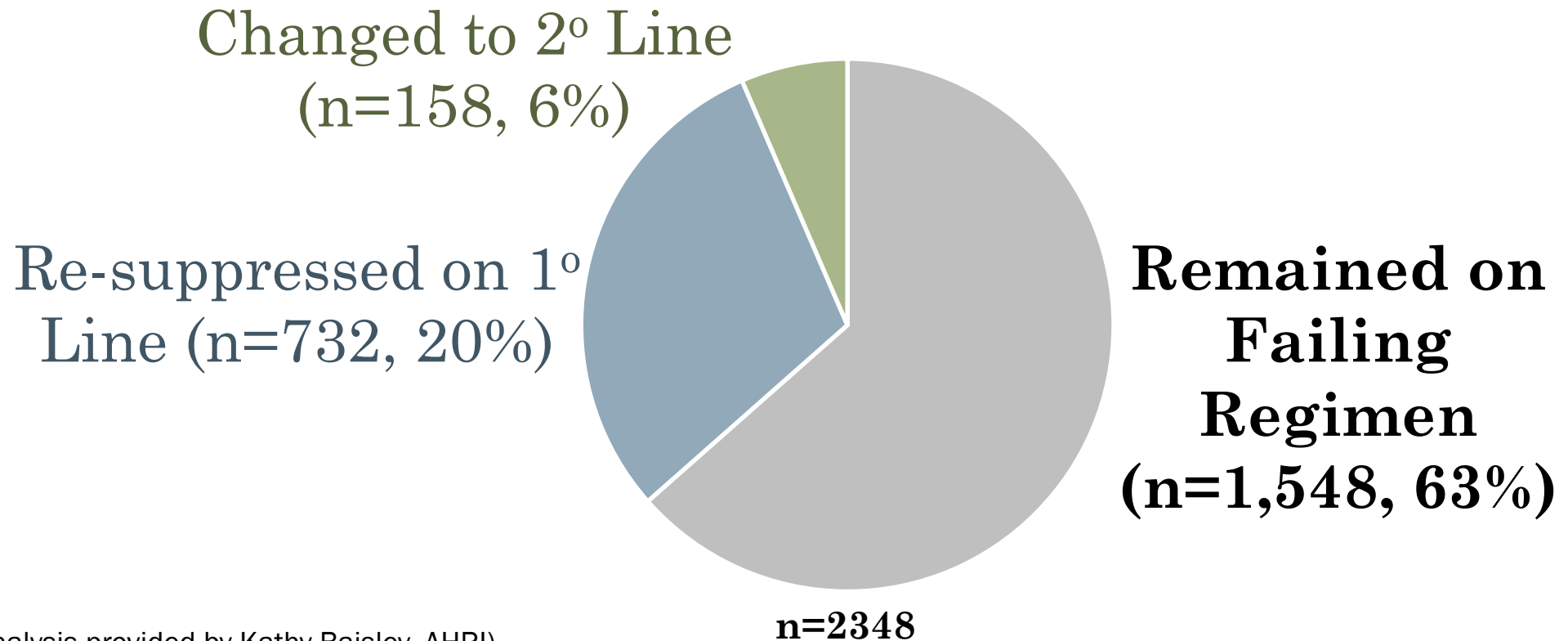
Last Update Posted ⓘ: February 13, 2018

See [Contacts and Locations](#)



# Resistance Testing Will Not Change Outcomes

- Can a resistance test be an adherence intervention for *clinicians*?

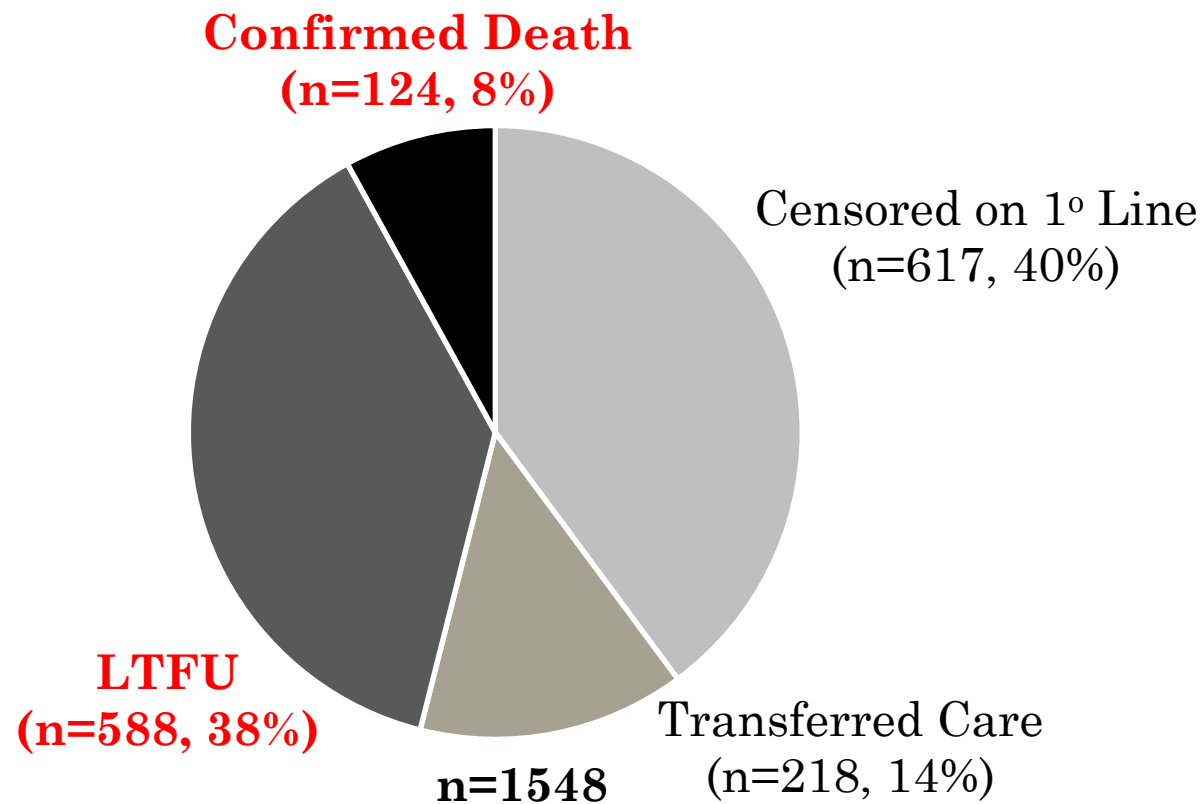
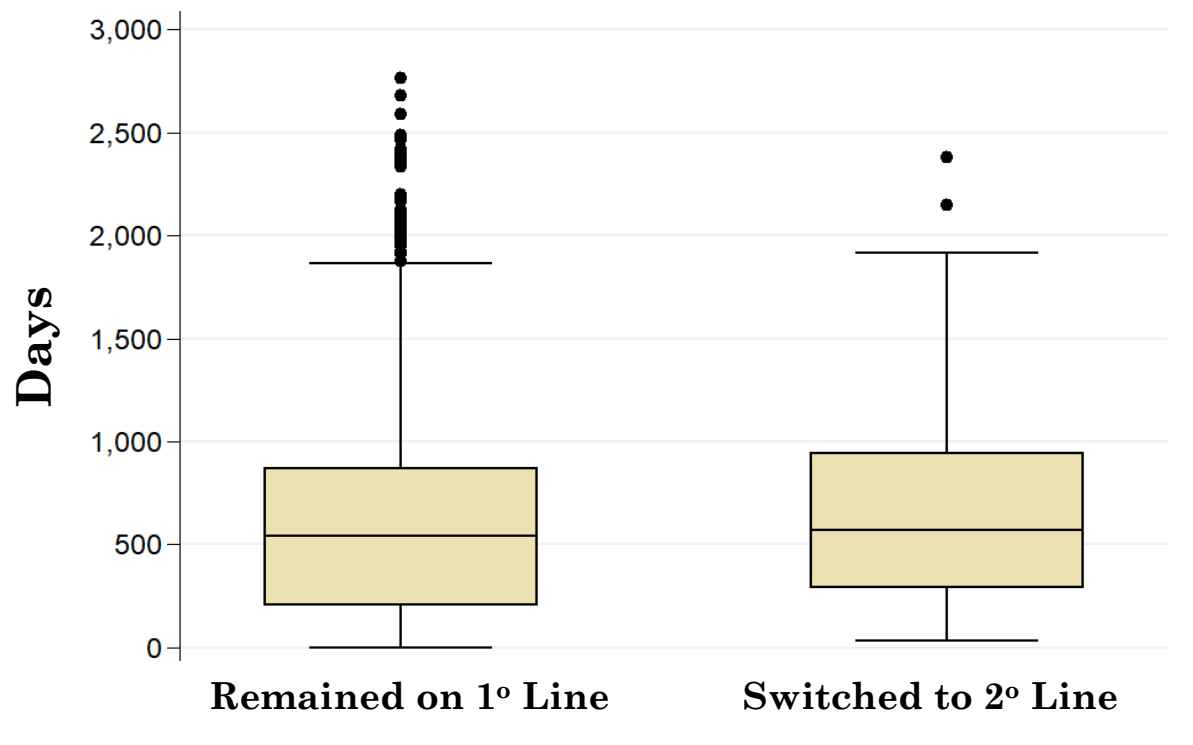




# Resistance Testing Will Not Change Outcomes

- Can a resistance test be an adherence intervention for *clinicians*?

## Days on a Failing Regimen



# A GRT is not necessarily a GRT

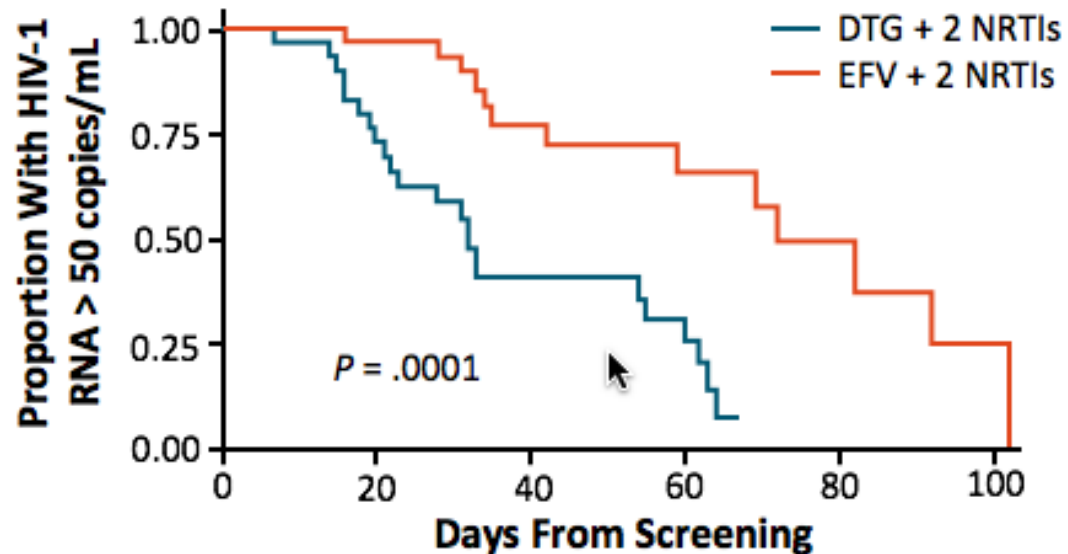
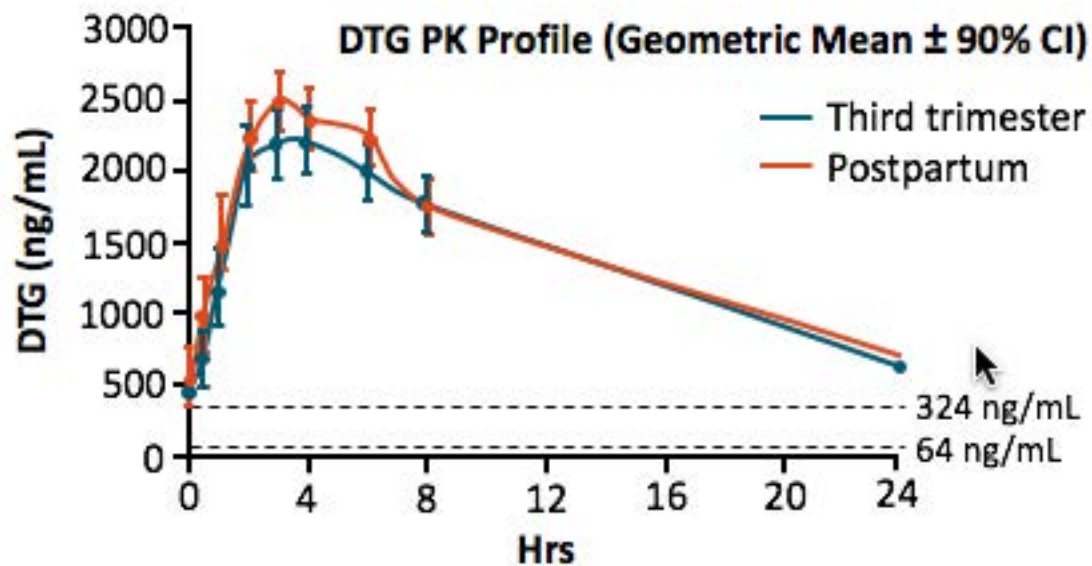
	<b>Pre DTG Era</b>	<b>Post DTG Era</b>
<b>Pre-ART GRT</b>	Case 1	Case 1
<b>GRT at First-Line Failure</b>	Case 2	Case 3

# Case 1

22 year old P1000 woman presents to care. She recently had a positive pregnancy test followed by a first ANC visit at ~10 weeks, where she was diagnosed with HIV. Her partner has been on treatment intermittently for 6 years with a one-pill/day regimen.

- a. Which initial HIV regimen would you choose in the *pre-DTG* era?
- b. Which initial HIV regimen would you choose in the *post-DTG* era
- c. Should a routine HIV resistance test be available in this case?

# Women presenting in pregnancy\*



## Case 2

30 year old man, diagnosed with HIV in 2017, presented with CD4 10, recently completed 6 months of drug-susceptible pulmonary TB therapy. Truck driver, and picks up his medicines consistently, but often away 2-3 months at a time. First VL six months into treatment 25,000 copies/mL. Claims excellent adherence.

- a. Should a routine HIV resistance test be available in this case?

## Case 3

42 year old woman, diagnosed with HIV in 2000. Previously treated with triple nucleoside regimen, then D4T/3TC/EFV, then TDF/FTC/EFV, then switched to DTG/TDF/3TC 18 months ago. She initially suppressed on that regimen, but now has had three detectable VL of approximately 10,000 copies/mL over the past 12 months. She has thrush and has lost 4 kilograms in the past 6 months.

- a. Which regimen would you choose?
- b. Should a routine HIV resistance test be available in this case?

# The Juice (might be) Worth the Squeeze

- Resistance is highly prevalent
  - Is resistance to INSTIs in SSA just a matter of time?
- Tradeoff between GRT and ART class step-up improving
- Resistance testing itself as an intervention to salvage lower cost-therapies
- Strong clinical rationale in key populations

# Thank you

- Suzanne McCluskey
- Kathy Baisley
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- Vince Marconi
- Ravi Gupta
- Kathy Baisley
- Francois Venter
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