REVAMP Clinical Trial:
Resistance Testing to Improve Management of Virologic Failure in sub-Saharan Africa

HIV Online Provider Education (HOPE) Conference
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On behalf of the REVAMP Study Team

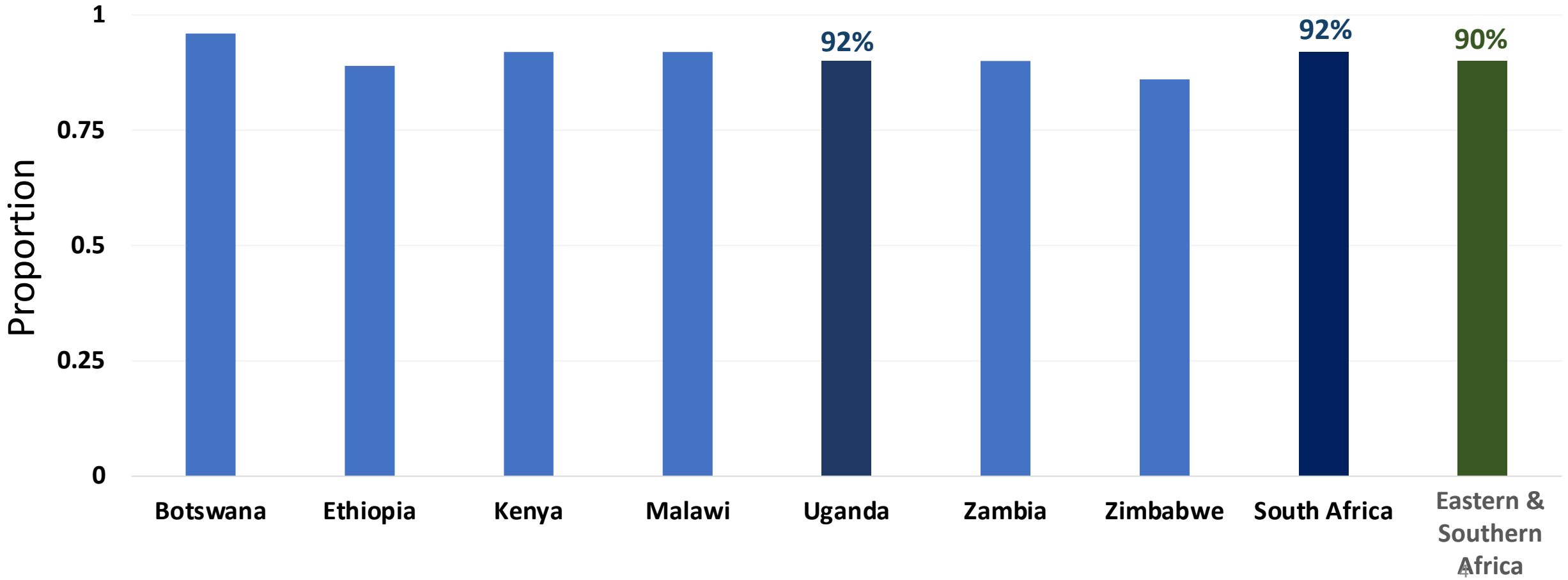
Conflicts and Disclosures

- REVAMP study was funded by the US National Institutes of Health and the President's Emergency Plan for AIDS Relief
- No other disclosures

Summary

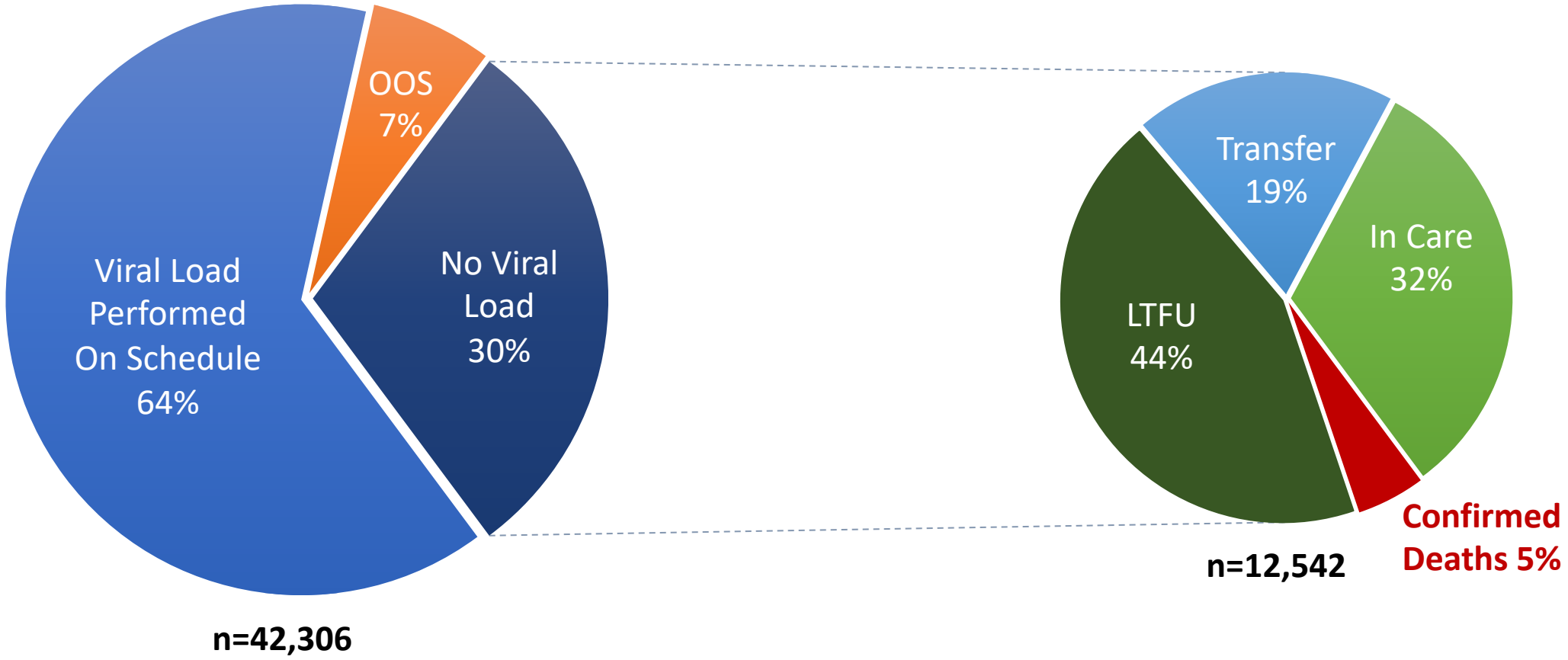
- Background
  - Epidemiology of virologic failure in sub-Saharan Africa
  - Evidence in support of HIV resistance testing at virologic failure
- Study design
- Primary results
- Secondary findings
- Discussion/questions

Suppression rates among those on ART: Eastern & South Africa



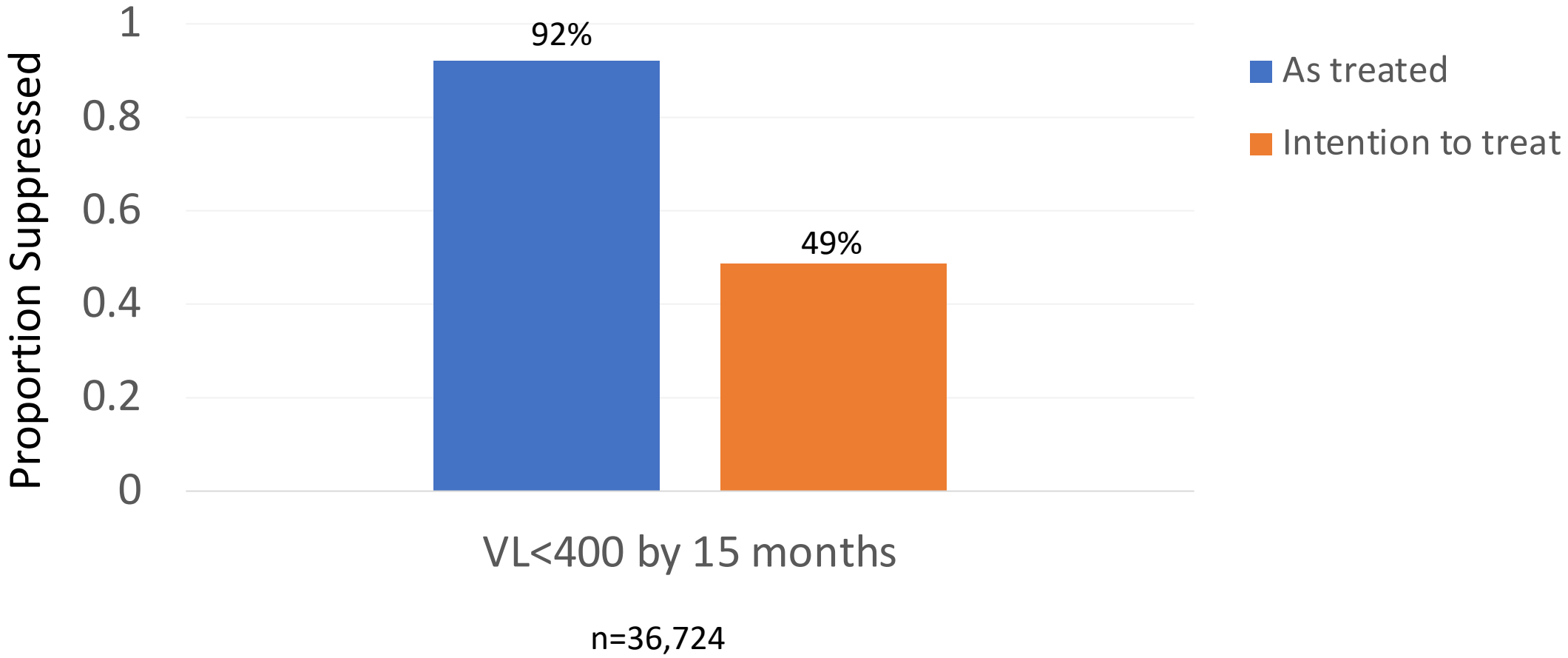
UNAIDS 2019

Virologic Monitoring after ART Initiation in Rural KwaZulu-Natal



Adapted from Iwuji et al, HIV Medicine, 2020

Virologic Suppression after ART Initiation in Rural KwaZulu-Natal



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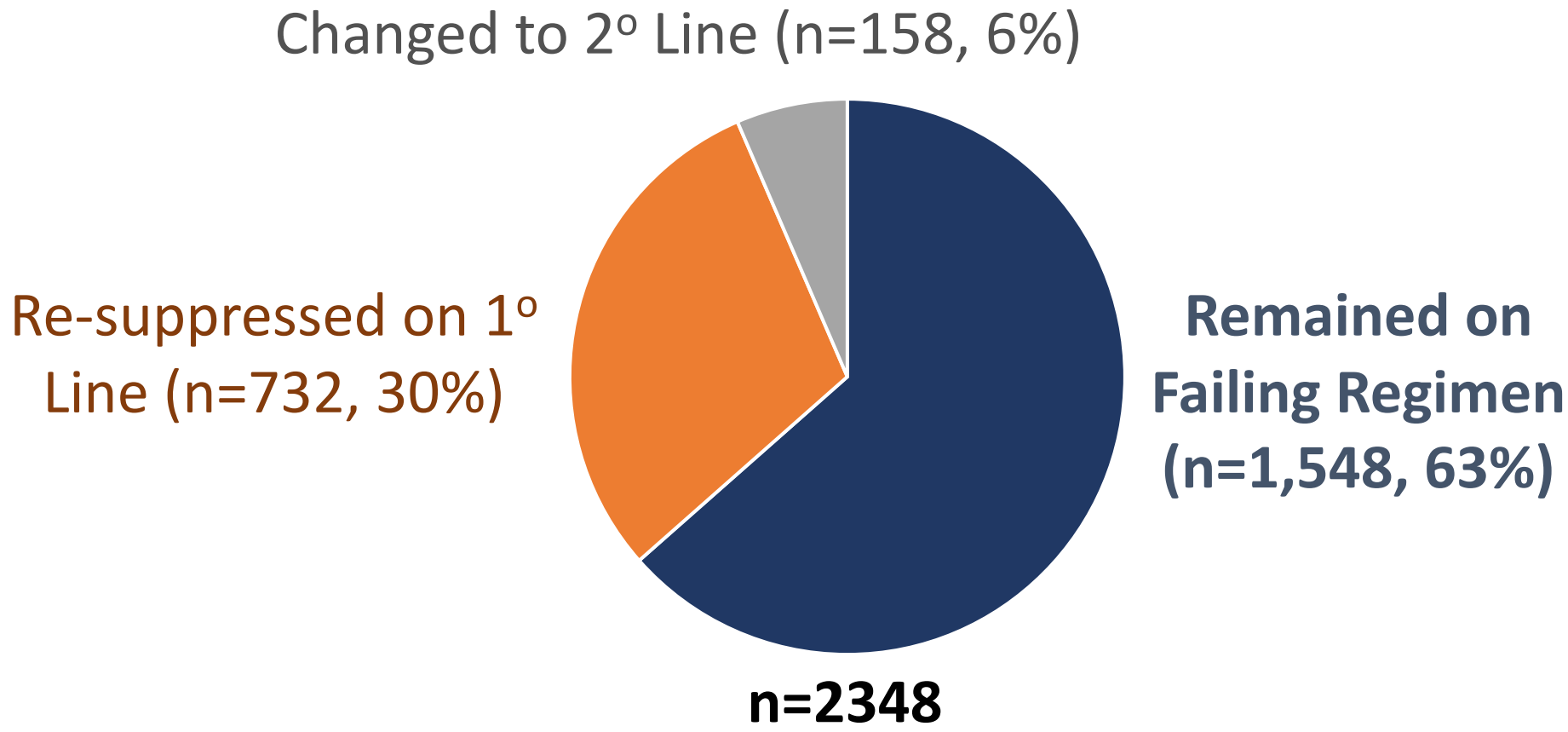
What happens to those on the wrong side of the “third 90”?



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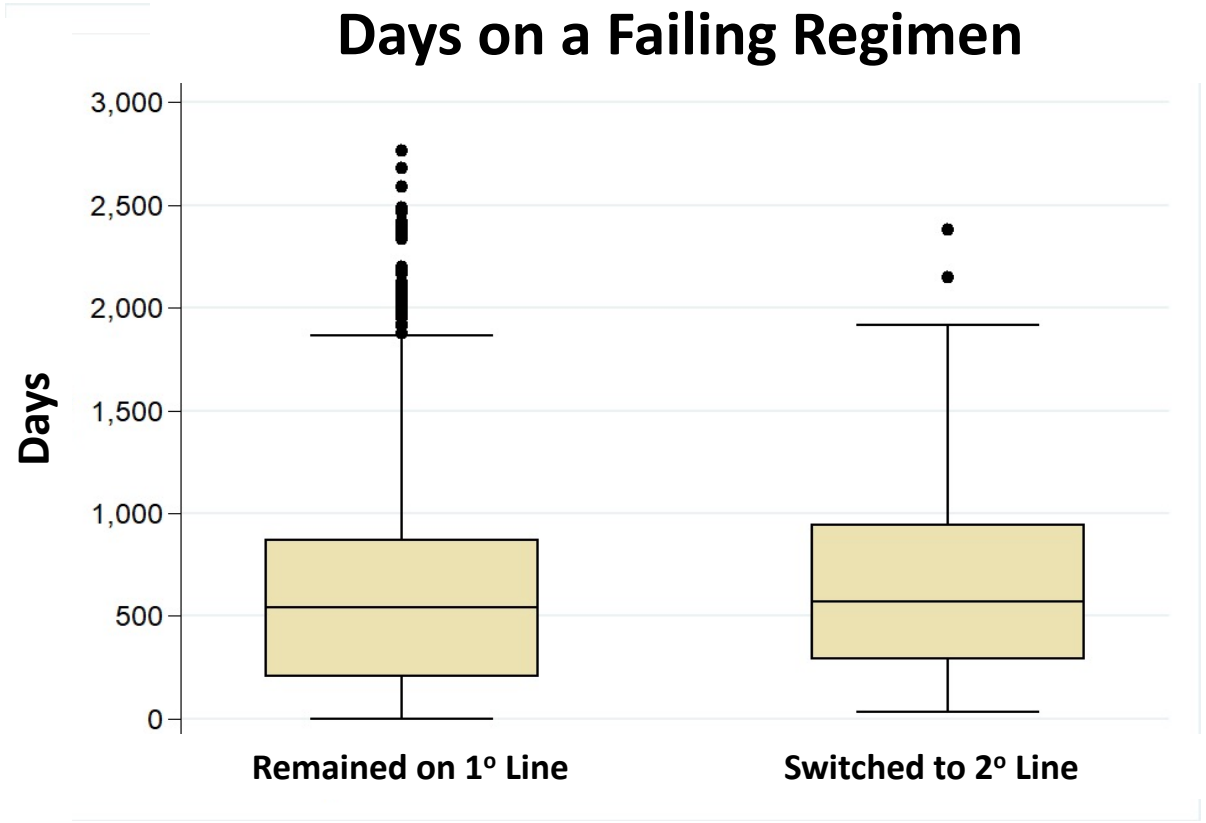

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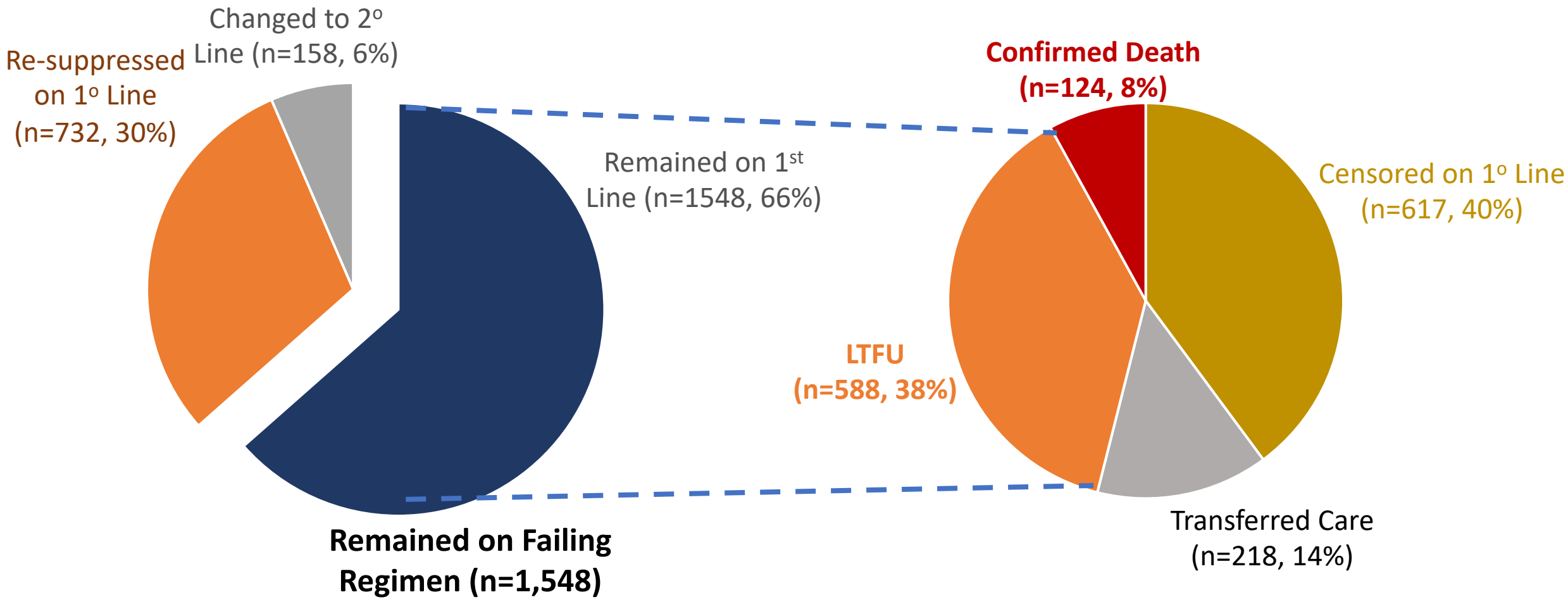

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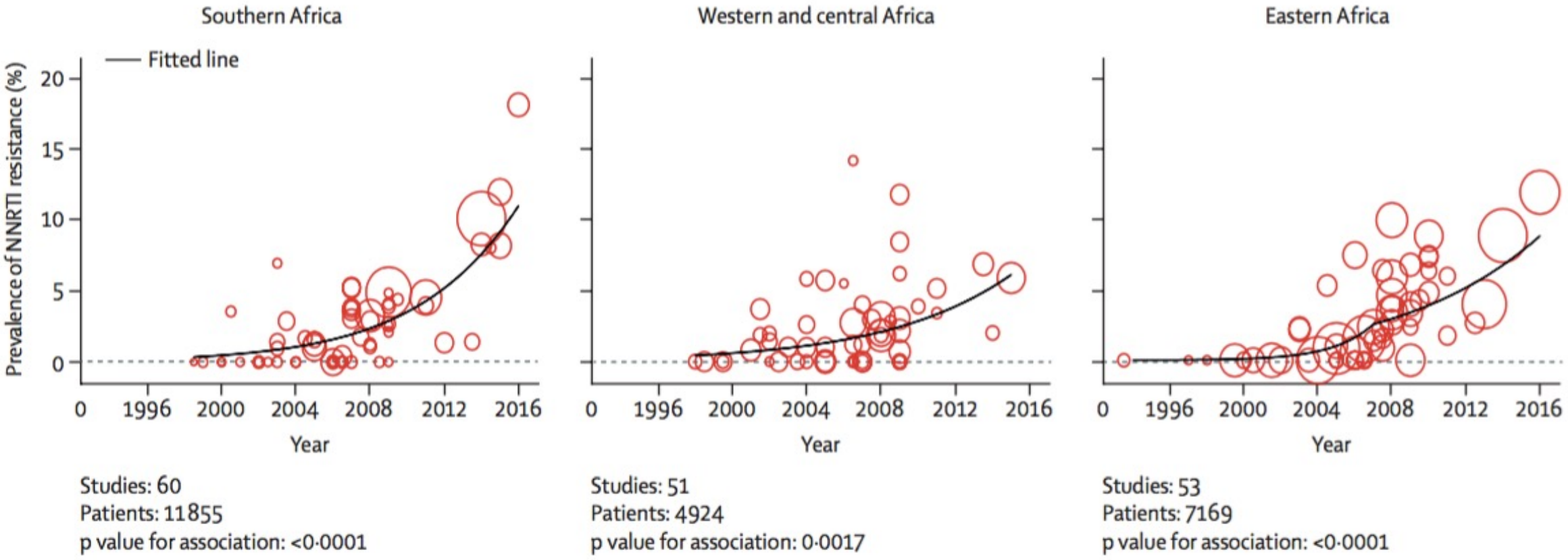


Gupta et al, Lancet HIV 2017

Epidemiology of Virologic Failure in sub-Saharan Africa

- Occurs in 10-30% initiating ART in sub-Saharan Africa
  - Likely under-reported programmatically with rates as high as 50% in as-treated analyses
- Those with virologic failure have extremely poor outcomes
  - Long delays between detection of failure and regimen change
  - High rates of LTFU
  - High rates of mortality
- Population level effects
  - Ongoing HIV transmission
  - Increasing rates of drug resistance

Management of Virologic Failure in sSA

- Guidelines differ, but most rely on a prolonged period of adherence counseling and repeated virologic monitoring
- None suggest resistance testing after first-line failure

Table 61: Criteria for switching ART due to treatment failure

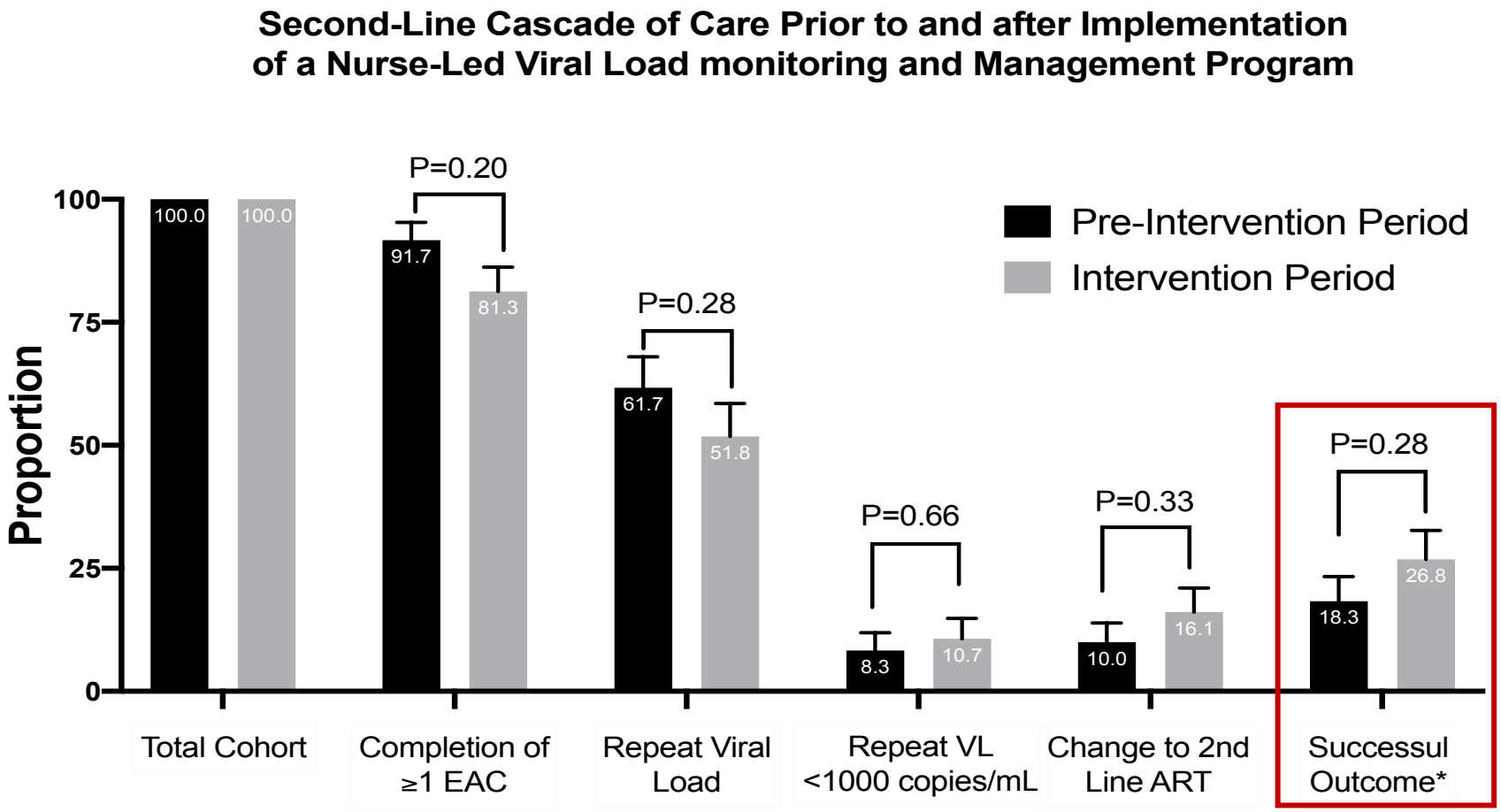
Failure	Definition	Comments
Each criterion below can be used independently to determine treatment failure. You do not need to have both to diagnose treatment failure.		
Virological failure	Two consecutive viral loads above 1000 copies/ml, done at least 3-6months apart, with adherence support following the 1st VL test.	The patient should have been on ART for at least six months

Consolidated HIV and AIDS Guidelines. Ugandan AIDS Commission, 2020.

How can we improve management of virologic failure?

- Optimal strategy is unknown, but would:
  - Reduce delays from virologic failure detection to management
  - Ensure active regimens initiated promptly
  - Support individuals through enhanced adherence counseling

Nurse-led intervention for VF in South Africa



*Successful outcome defined as a repeat VL <1000 copies/mL or a change to second= line ART after a repeat VL>1000 copies/mL within 6 months of first-line ART virologic failure

Sunpath et al, S Afr Med J, 2021

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  - Reduce delays from virologic failure detection to management
  - Ensure active regimens initiated promptly
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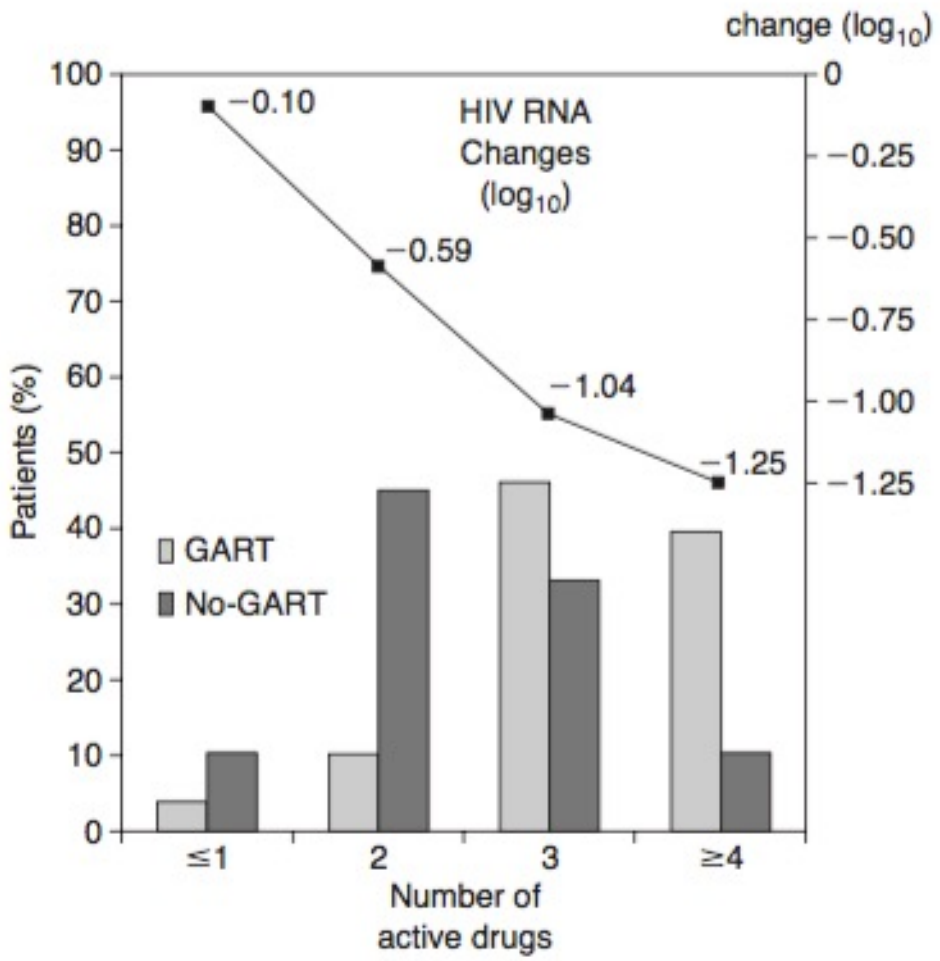
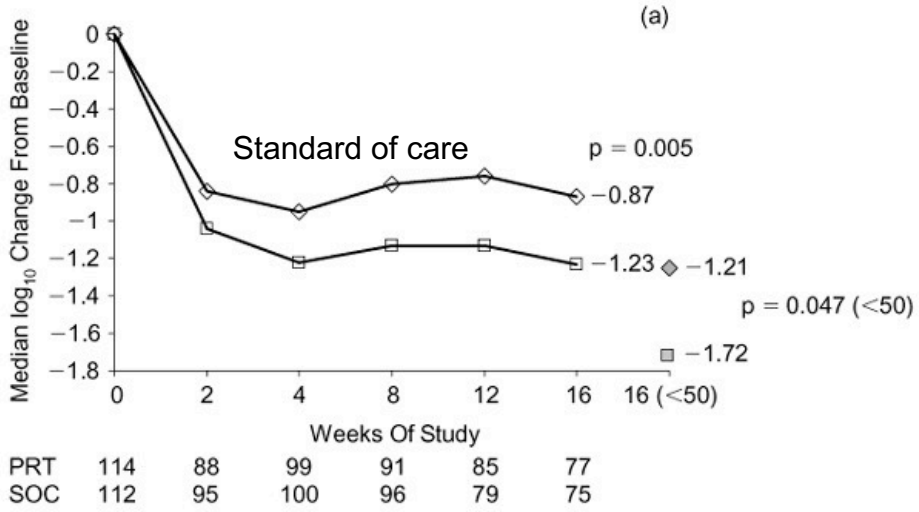
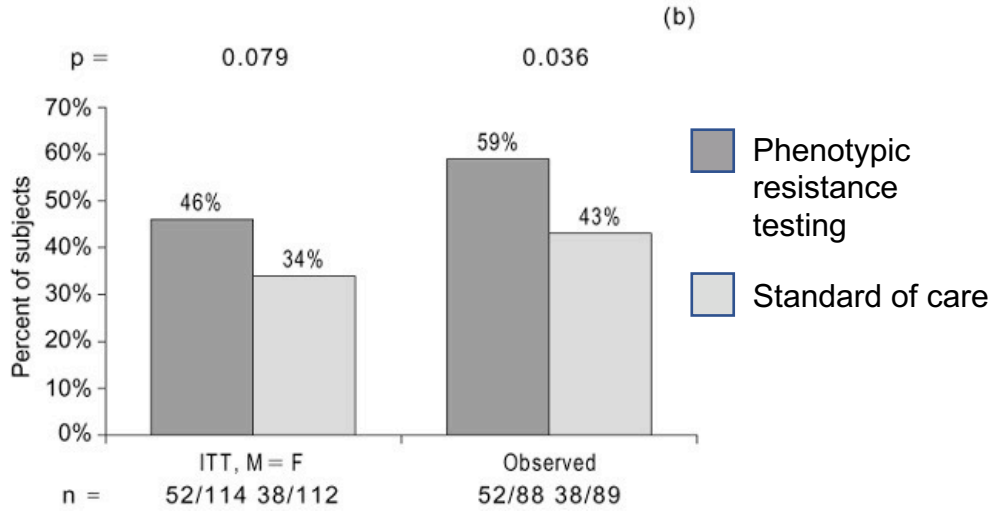
- **HIV drug resistance testing is cornerstone of management in high-income countries**

DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. 2020

Resistance testing to improve management of HIV virologic failure







Baxter et al, AIDS, 2000
Cohen et al, AIDS, 2002

Cost effectiveness of resistance testing in resource limited settings

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	**Very cost effective**
Cost minimization model [25]	South Africa	Presumed Payer	5 years	Cost per strategy	Deterministic/ Probabilistic	**Cost Neutral**
HIV synthesis transmission individual-based stochastic model [26]	Zimbabwe	Unstated	10 years	Cost/ disability adjusted life year (DALY) averted	Several one way sensitivity analyses	**Not cost-effective**

Levison et al, *Clin Infect Dis*, 2013
Rosen et al, *J Int AIDS Soc,* 2011
Phillips et al, *PLoS One*, 2014

Potential advantages of resistance testing model of care

- Expedited management of virologic failure
- Decreasing costs of genotypic resistance testing in comparison to second-line regimens in sSA
- Resistance testing as an adherence intervention
  - An “objective” adherence test and teachable moment for patient-clinician encounter
  - Perceived value of enhanced care

REVAMP Trial: Objectives

- Determine the effectiveness and cost-effectiveness of genotypic resistance testing to improve management of HIV virologic failure in public sector in sub-Saharan Africa

REVAMP Trial: Design & Setting

- Open-label randomized, pragmatic clinical trial

- Five public sector HIV clinics
  - Durban, South Africa
    - Wentworth Hospital. HIV Clinic
    - King Dinizulu HIV Clinic
    - Clairwood Hospital HIV Clinic
    - Addington Hospital Sinathando HIV Clinic
  - Mbarara, Uganda
    - Mbarara Regional Referral Hospital Immune Suppression Syndrome Clinic

Siedner et al, HIV Clin Trials, 2017

REVAMP Trial: Inclusion Criteria

- Inclusion criteria:
  - Age > 18 years old
  - First-line ART for ≥5 months
  - HIV viral load >1,000 copies/mL in prior 90 days
  - No prior protease inhibitor exposure
  - No prior known drug resistance

- Exclusion criteria:
  - Declined consent
  - Plans to leave catchment area/clinic in next 9 months

Siedner et al, HIV Clin Trials, 2017

REVAMP Trial: Randomization

- 1:1 randomization to standard of care versus immediate resistance testing strategies
- Randomization stratified by:
  - Clinic
  - Pregnancy status
  - ART duration of less than or greater than 1 year
  - Use of INSTI vs NNRTI in first-line (NB: no participants enrolled on INSTI)
- Blocked into groups of 10

Siedner et al, HIV Clin Trials, 2017

REVAMP Trial: Intervention

- All study clinics underwent resistance testing interpretation training by Dr. Kevin Ard
- Immediate genotypic resistance testing upon enrollment
  - RT gene sequencing
  - JCRC in Entebbe, Uganda
  - Inkosi Albert Luthuli NHLS Laboratory in Durban, SA

GUIDEBOK PURPOSE

The purpose of this manual is to summarize the most common antiretroviral resistance mutations that occur upon failure of first-line antiretroviral therapy and to make recommendations about antiretroviral treatment in the context of these mutations.

GUIDEBOOK ORGANIZATION AND TABLE FORMAT

The manual is organized by current antiretroviral regimen, which can be found on the header of each page:

CURRENT REGIMEN: TDF/3TC(FTC)/EFV
Tenofovir + lamivudine (or emtricitabine) + efavirenz

Recommendations are listed separately for situations in which a single mutation is present versus multiple mutations. If only one mutation is identified on the participant's resistance test, refer to the table addressing management in the context of solitary drug mutations. Otherwise, refer to the table addressing management in the context of multiple mutations.

Once the correct table has been identified, locate the mutation or mutations in the table's left-hand column that corresponds to the mutation or mutations listed in the participant's resistance genotype. Read across the row to see drugs affected by the identified mutations, suggested drugs to stop, and recommended new regimens. By convention, mutations are denoted by a letter, followed by a number, followed by a second letter; together, the letters and number denote the position and type of amino acid substitution that confers resistance. Importantly, the letters and numbers on the genotype must match those in the table exactly in order to follow the recommendations outlined in the table.

Mutations	Drugs with reduced susceptibility	Suggested response	New regimen
M184V,I	3TC(FTC), ABC	Stop EFV, start LPV/r or ATV/r, continue TDF/3TC(FTC)	TDF/3TC(FTC)/LPV/r or TDF/3TC(FTC)/ATV/r

Mutations

Drugs affected by mutation

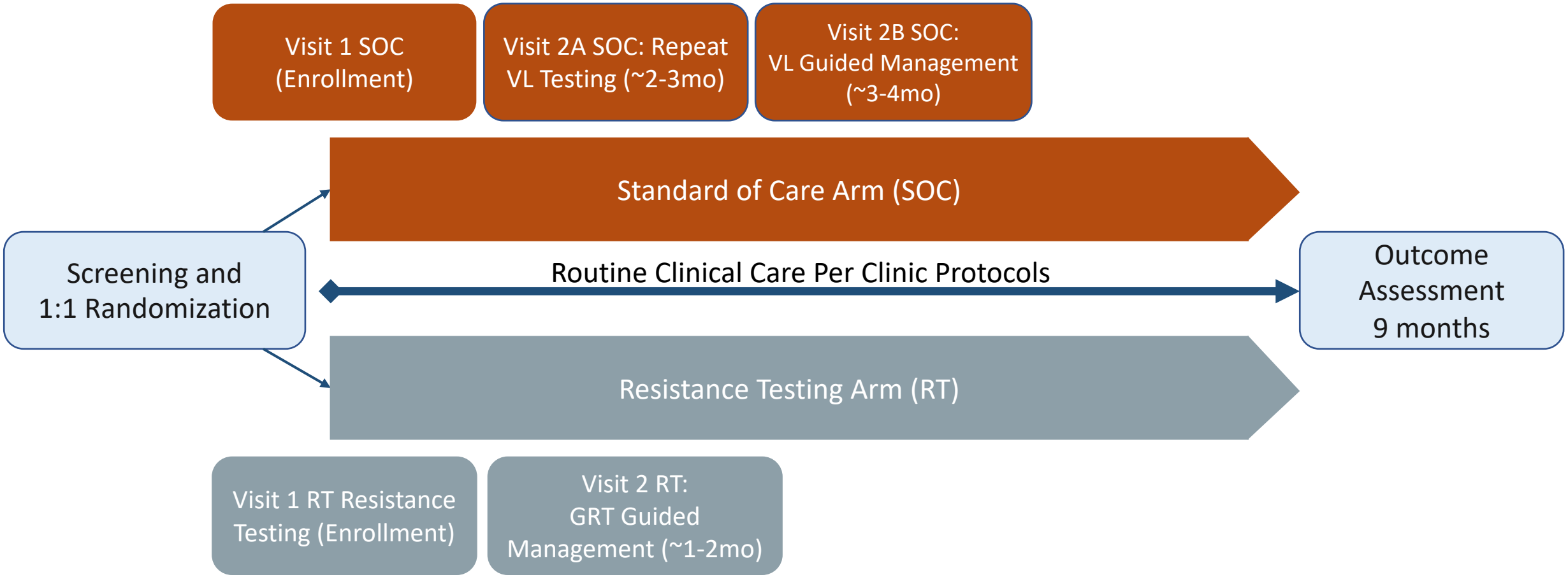
Suggested drugs to stop

Suggested new regimens

A table of common NRTI and NNRTI mutations is included at the end of this guidebook for reference.

Siedner et al, HIV Clin Trials, 2017

REVAMP Trial: Study Flow



REVAMP Trial: Statistical Analysis

- Primary outcome
  - Achievement of viral load < 200 copies/mL 9 months after enrollment
  - Loss from observation and death assessed as failure
- Secondary outcomes
  - Achievement of viral load below limit of assay
  - Achievement of suppressed viral load on first-line therapy
  - Proportion with IAS-USA defined resistance at study conclusion
  - Loss from observation
  - 9-month cumulative mortality
- Powered to detect 10% difference in primary outcome between arms
  - All analyses as intention to treat using superiority design

Siedner et al, HIV Clin Trials, 2017

REVAMP Trial: Cohort Characteristics

Characteristic	Standard of Care (SOC) (n=423)	Genotypic Resistance Testing (GRT) (n=417)
Enrolled in Uganda (n, %)	210 (50%)	210 (50%)
Age (median, IQR)	37 (31-45)	37 (30-44)
Female sex (n, %)	221 (53%)	209 (50%)

Siedner et al, CROI, 2021

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Female sex (n, %)	221 (53%)	209 (50%)
Years of ART (median, IQR)	3.5 (1.1-6.5)	3.0 (1.1-6.4)
CD4 count (median, IQR)	303 (132-475)	259 (112-434)
Enrollment ART Regimen		
TDF/3(F)TC/EFV	311 (75%)	295 (71%)
AZT/3TC/NVP	60 (14%)	58 (14%)

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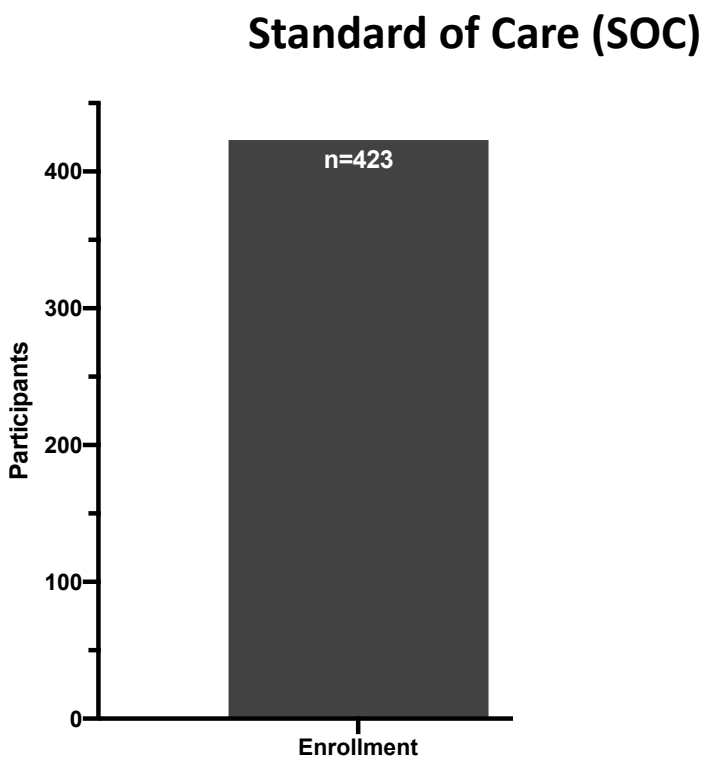
Pregnant at enrollment (n, %)	7 (2%)	6 (1%)

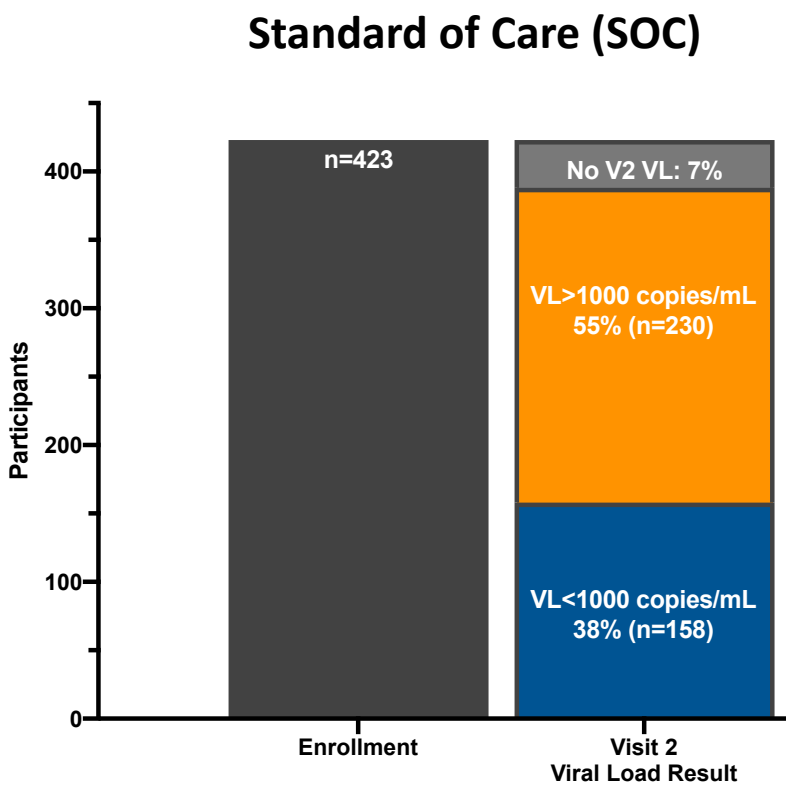
Siedner et al, CROI, 2021

REVAMP Trial: Fidelity to Interventions



Siedner et al, CROI, 2021

REVAMP Trial: Flow of Participants



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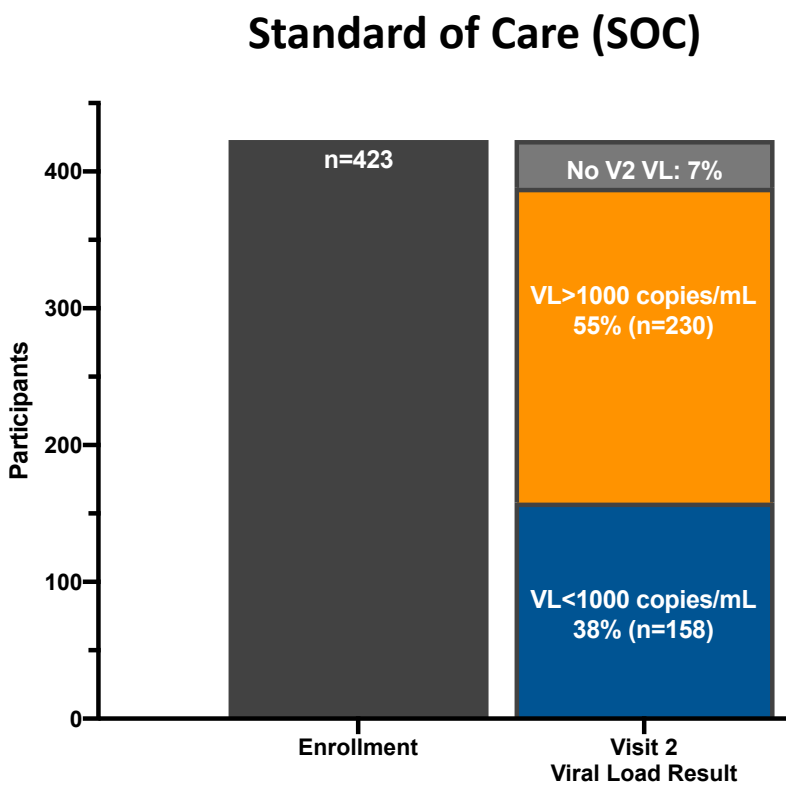

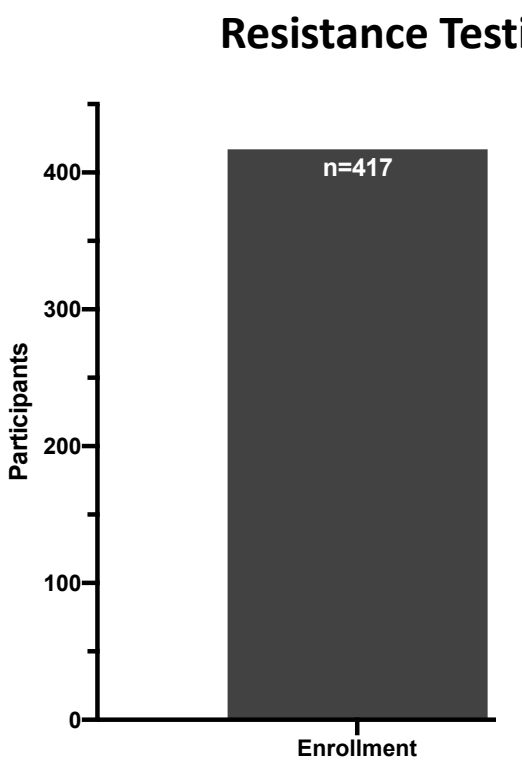

Siedner et al, CROI, 2021

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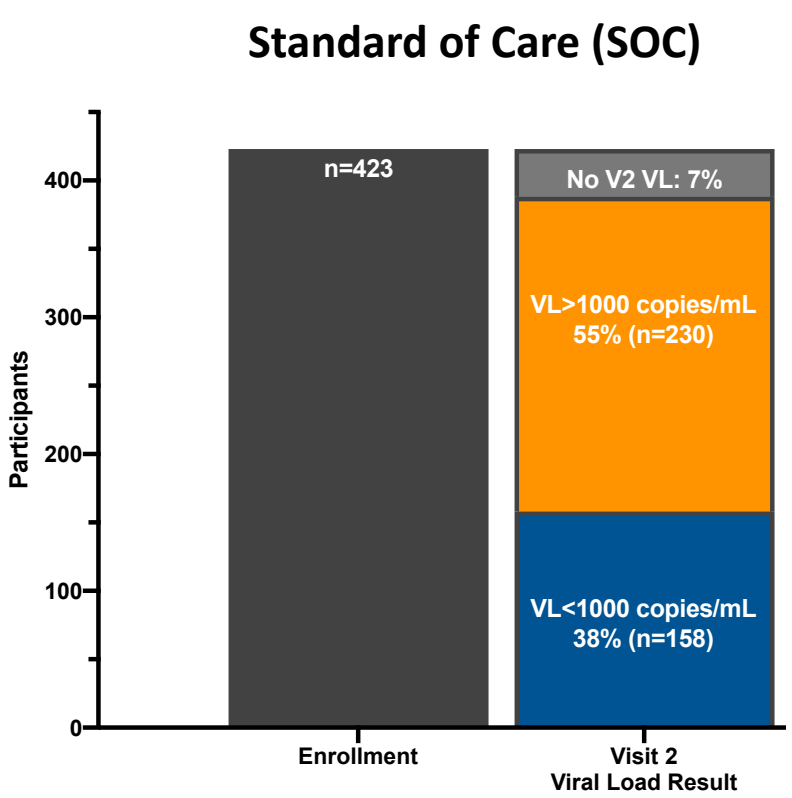
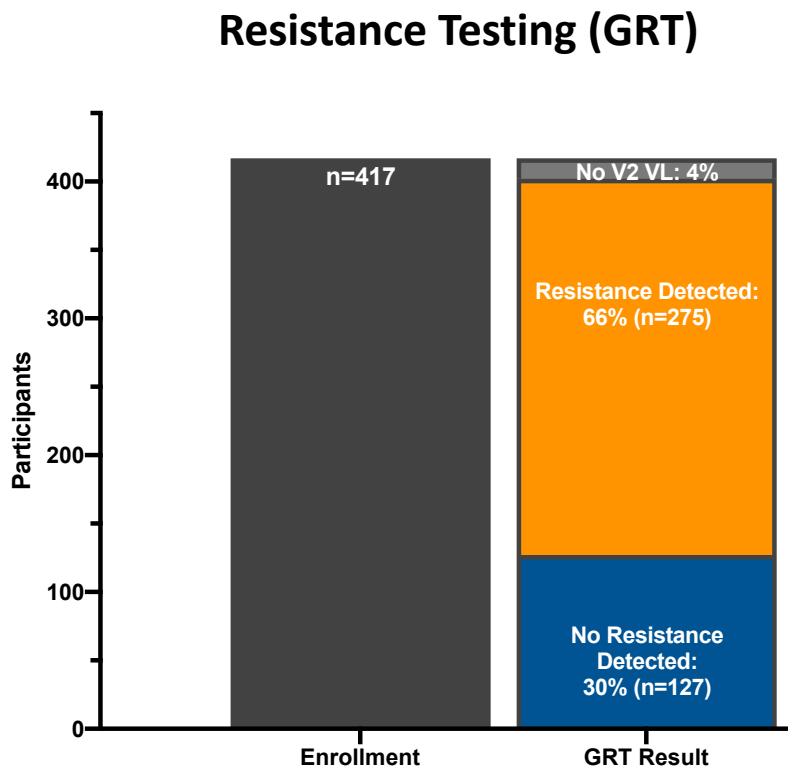
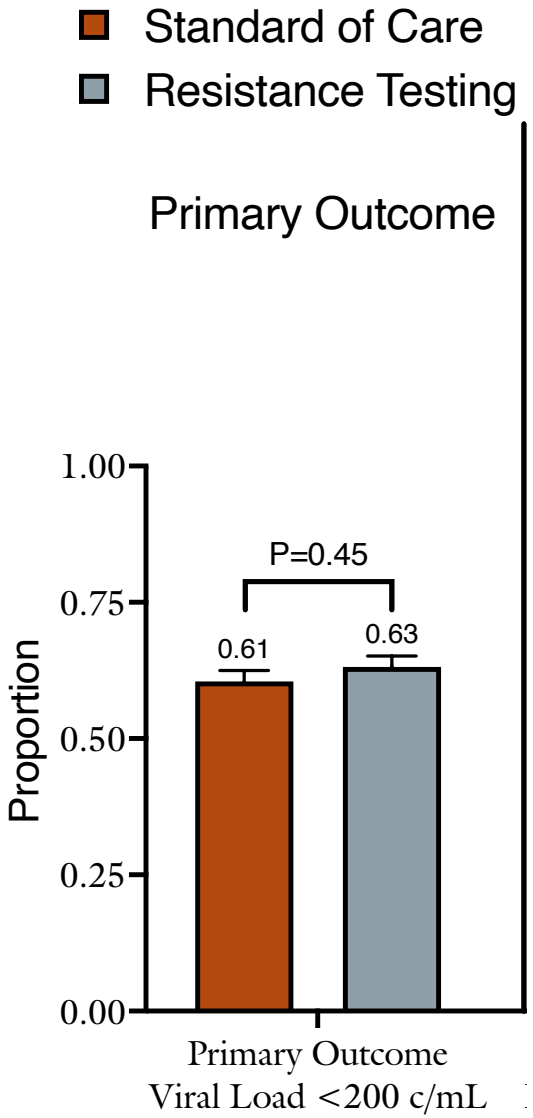




Siedner et al, CROI, 2021

REVAMP Trial: Primary & Secondary Outcomes



Siedner et al, CROI, 2021

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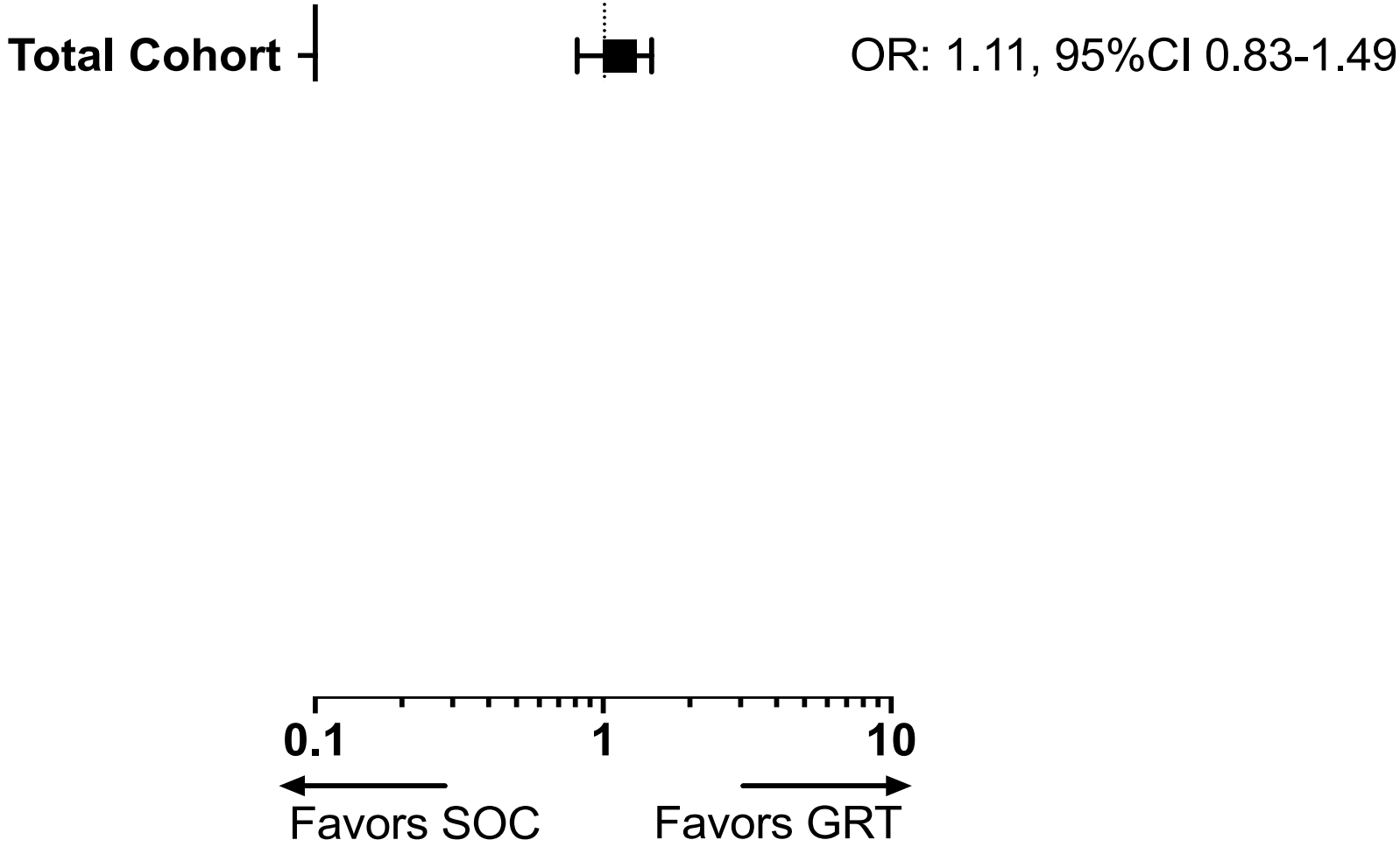

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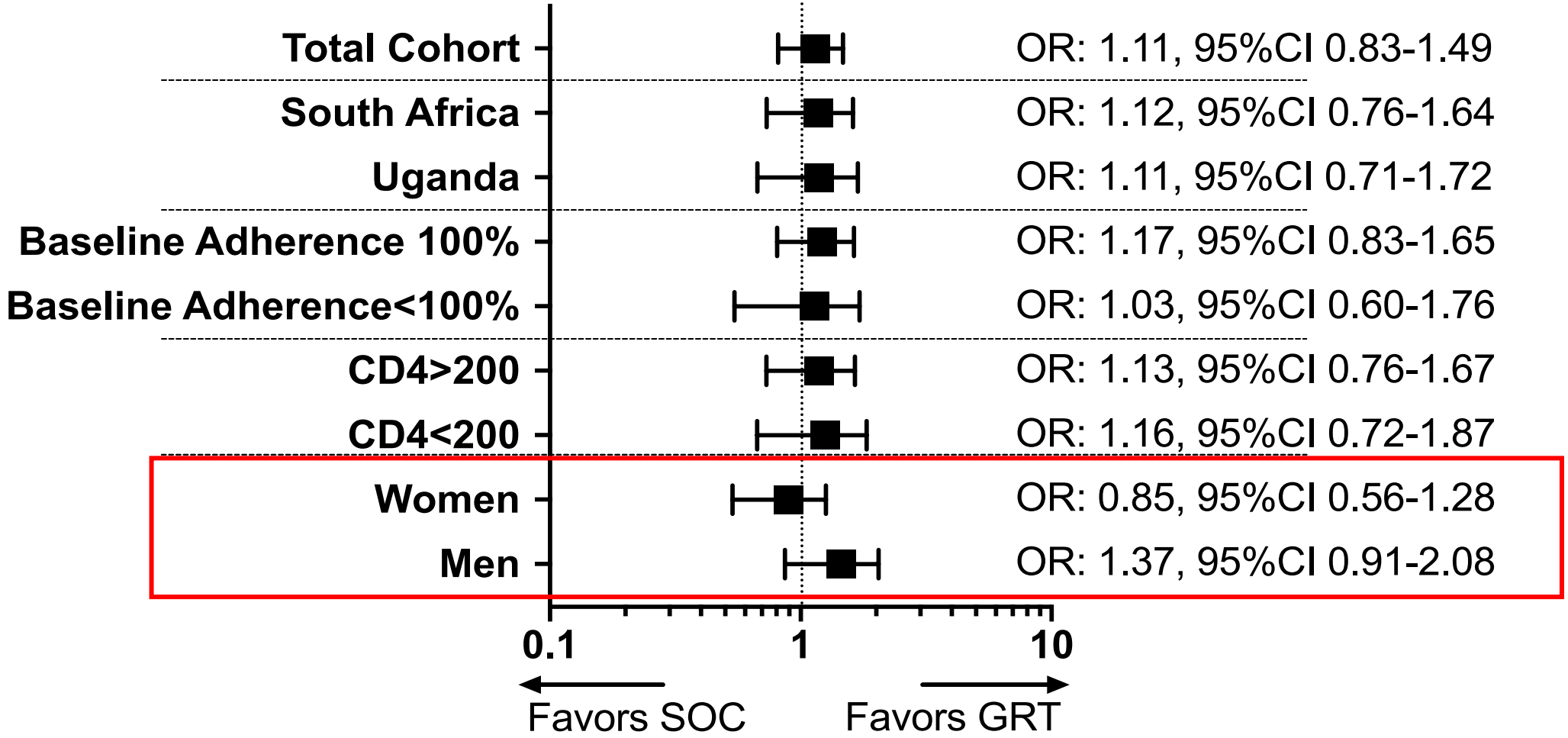
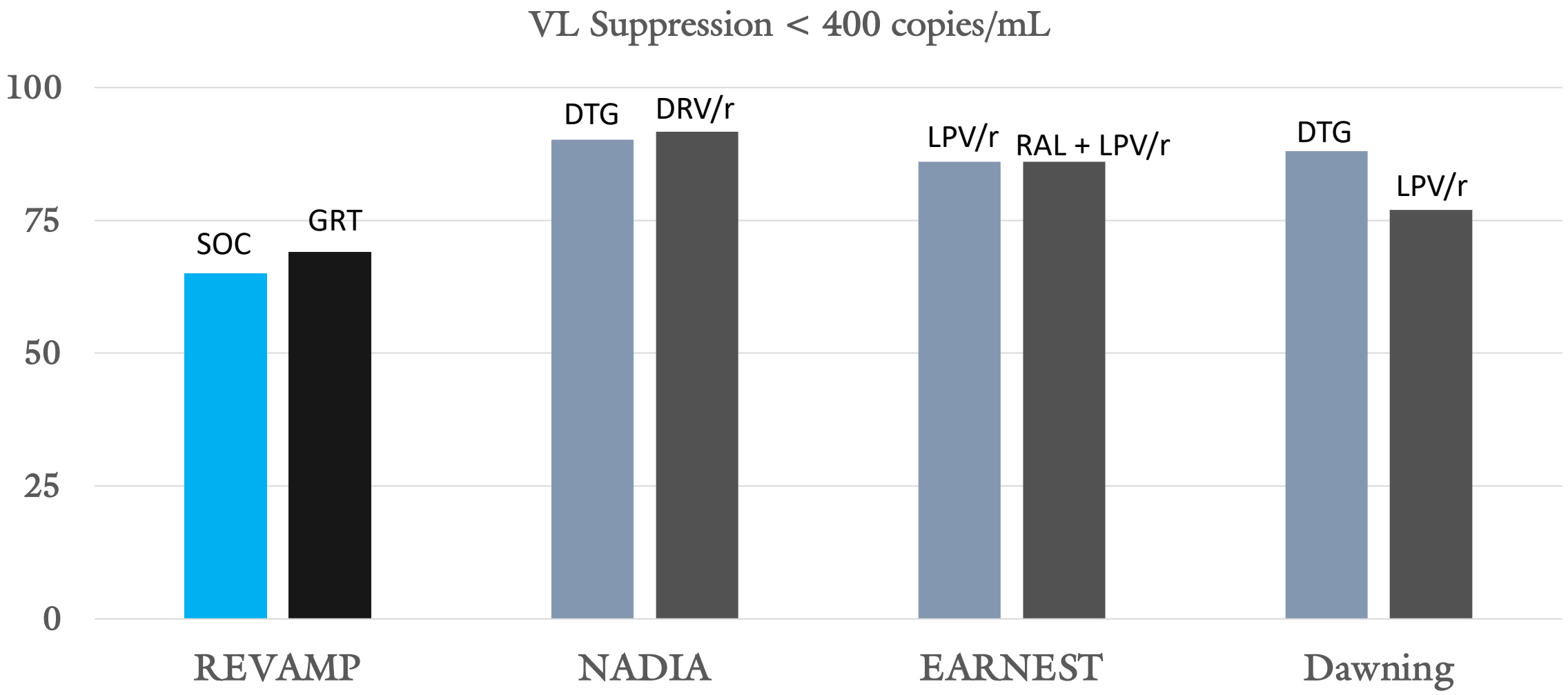


Siedner et al, CROI, 2021

Comparison to other second-line studies

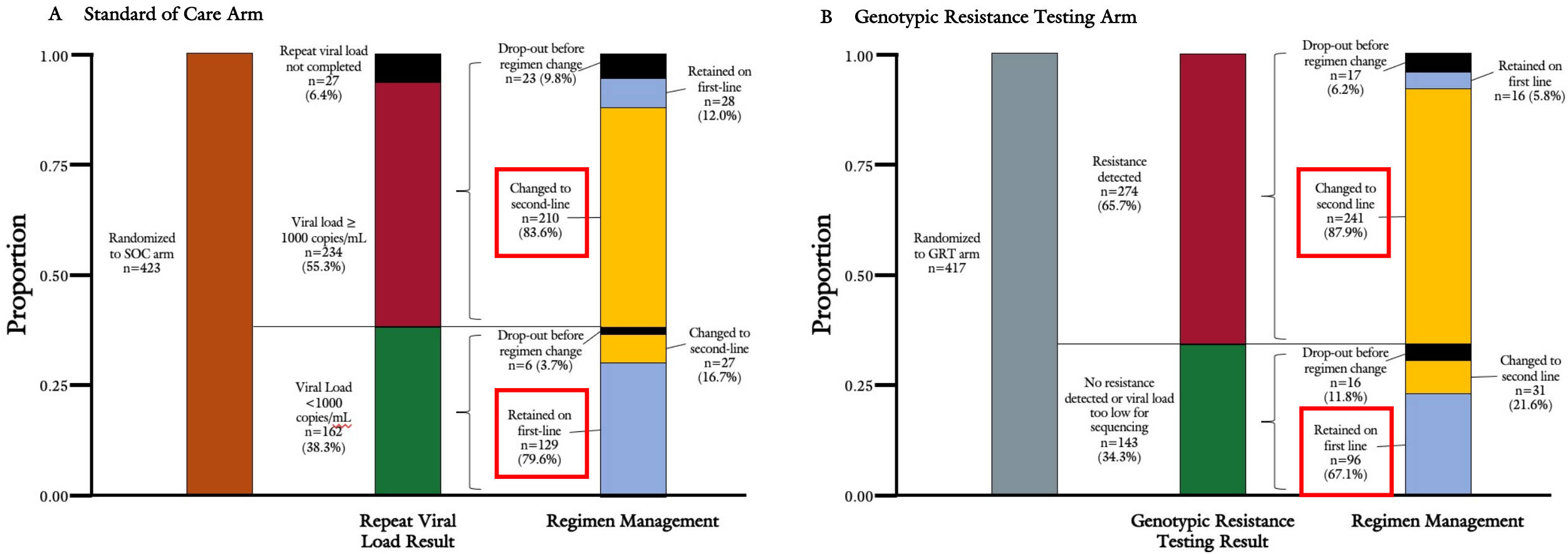


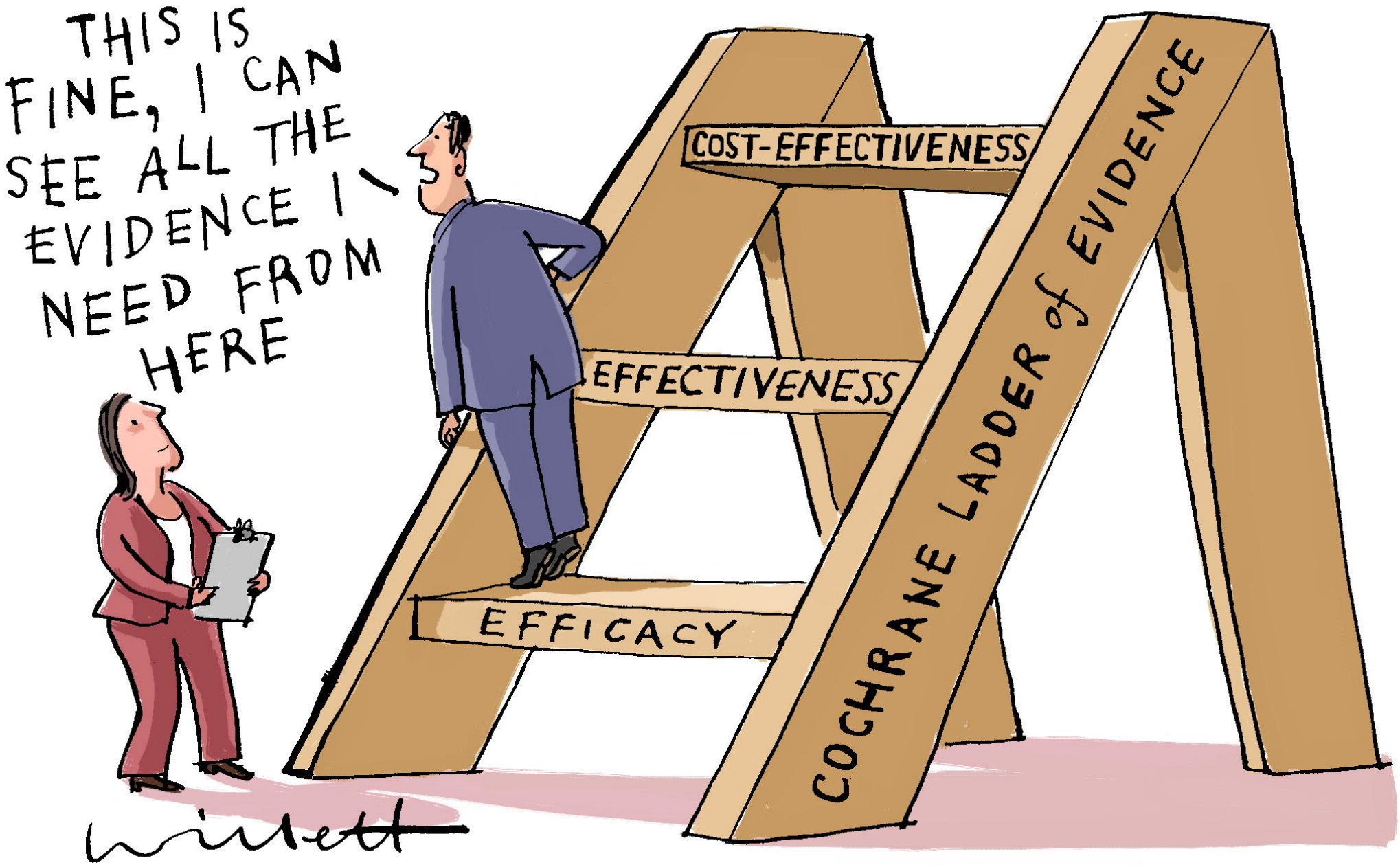
REVAMP Trial: Effectiveness Design?

- Study operated fully through public sector study clinics and laboratories
  - Provided lab results and GRT training
  - All treatment decisions ultimately left to clinic staff

- However,
  - 100% successful completion of resistance testing in GRT arm
  - High study completion rates
    - 93% completed study
    - 1% disenrolled
    - 1% transferred out
    - 3% LTFU
    - 3% deceased

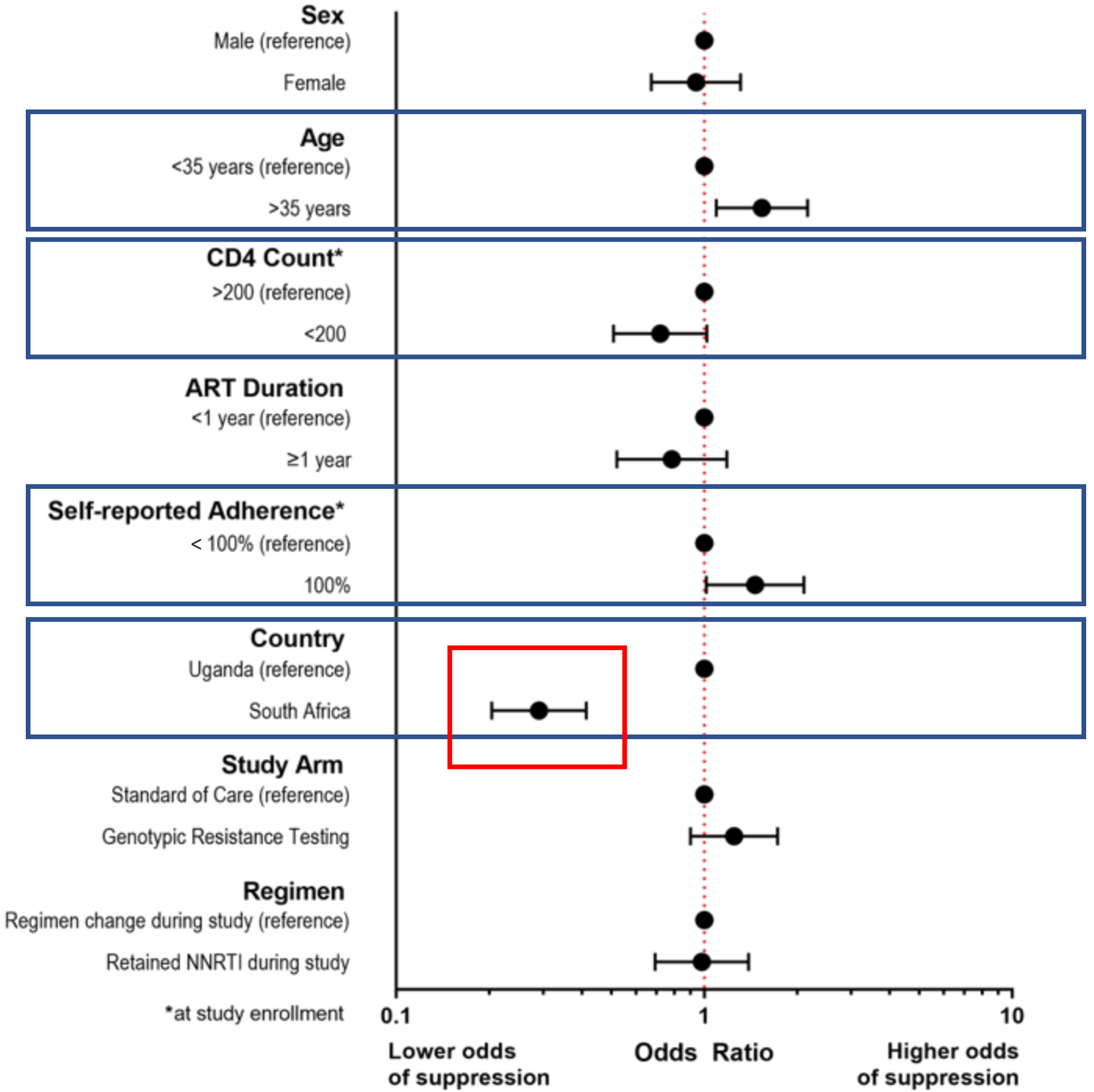
REVAMP Trial: Fidelity to Interventions




THIS IS FINE, I CAN SEE ALL THE EVIDENCE I NEED FROM HERE
COST-EFFECTIVENESS
EFFECTIVENESS
EFFICACY
COCHRANE LADDER of EVIDENCE
willett

Secondary findings

- If GRT did not predict virologic suppression, did anything else?



Predictors of Re-suppression

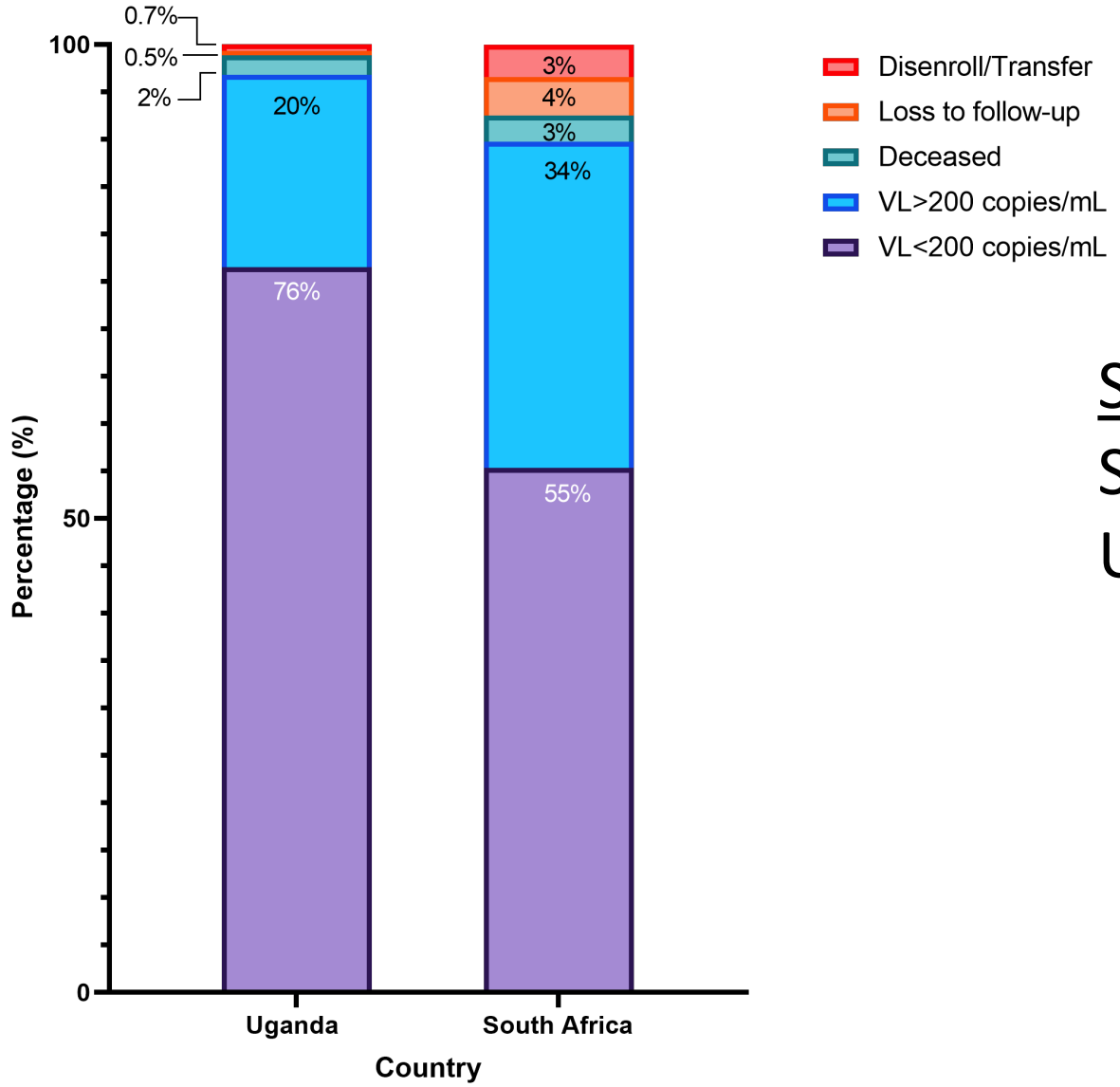
Age >35

CD4>200

Adherence=100%

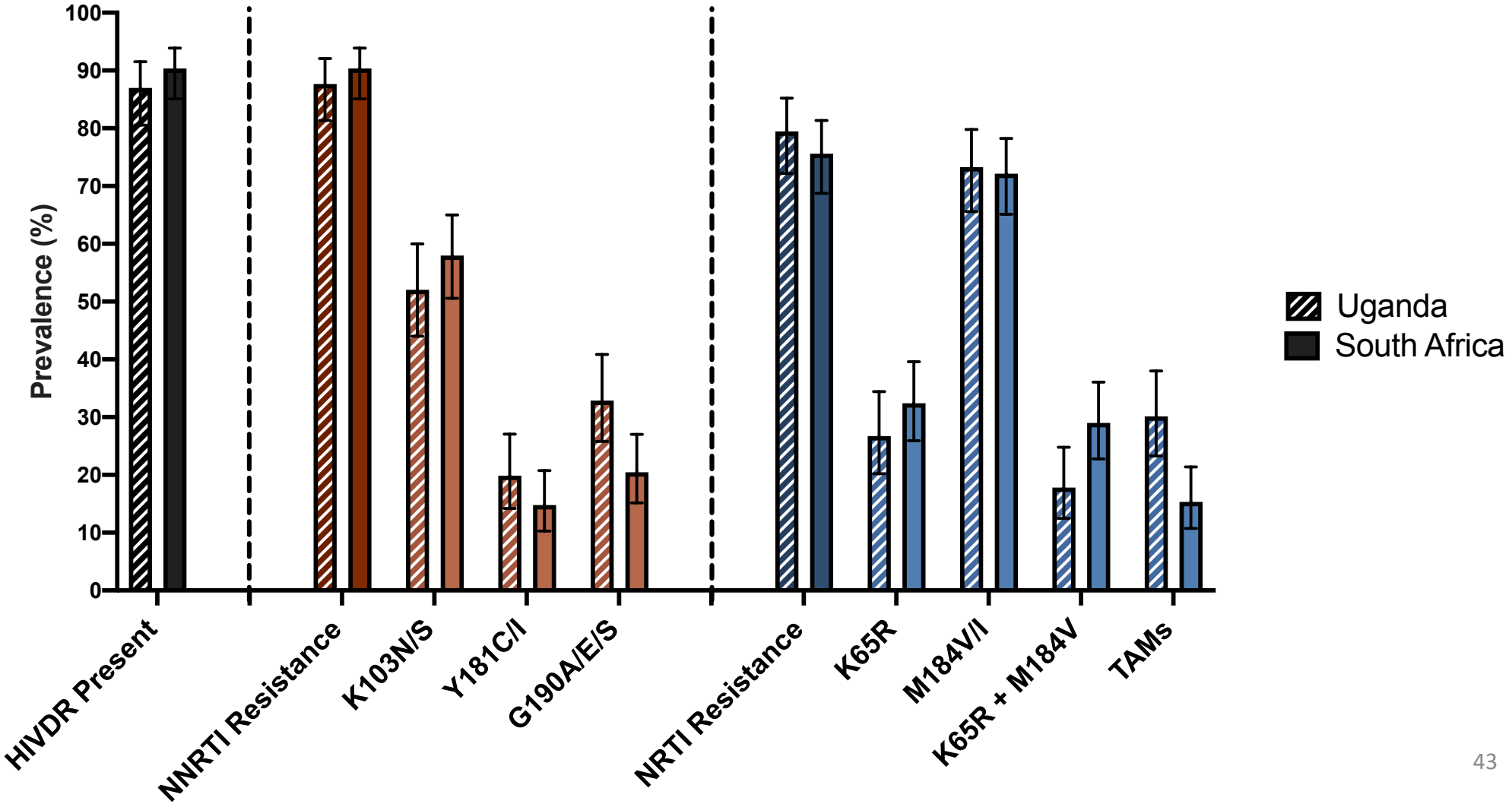
Uganda vs SA

Outcomes of Participants in Standard of Care Arm



<u>Suppression rate</u>:
South Africa 55%
Uganda 76%

Resistance patterns by site



Demographic differences by country

Factor	Uganda (n=420)	South Africa (n=420)	P-value
Most recent CD4 count			
<200	25.7%	45.5%	<0.001
200-500	35.7%	40.5%	
>500	38.6%	14.1%	

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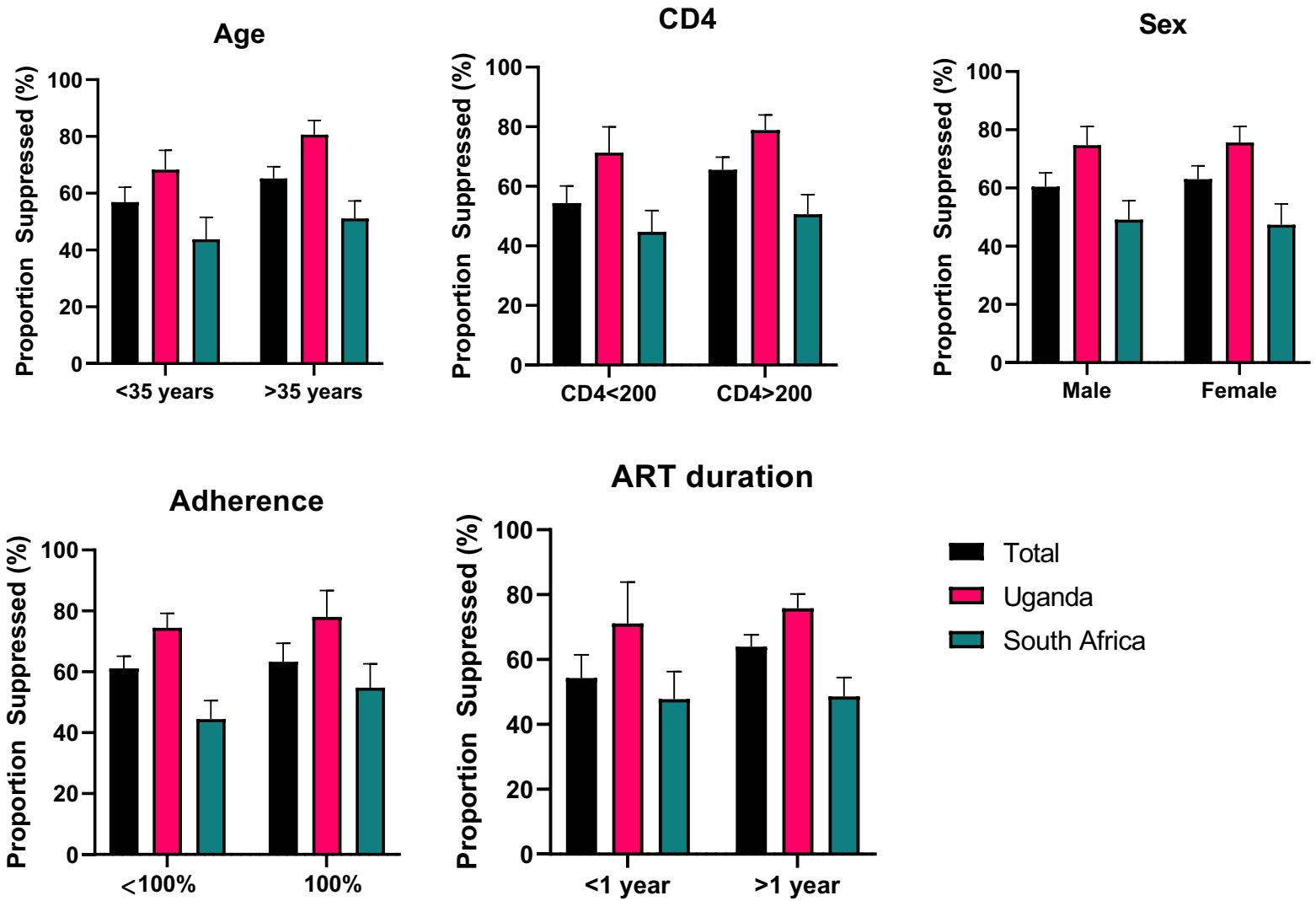
Most recent CD4 count			
<200	25.7%	45.5%	<0.001
200-500	35.7%	40.5%	
>500	38.6%	14.1%	
Current or prior opportunistic infection	20.2%	51.2%	<0.001

- **44% of OIs TB in SA**
- **13% of OIs TB in Ug**

Outcomes by country and risk factors



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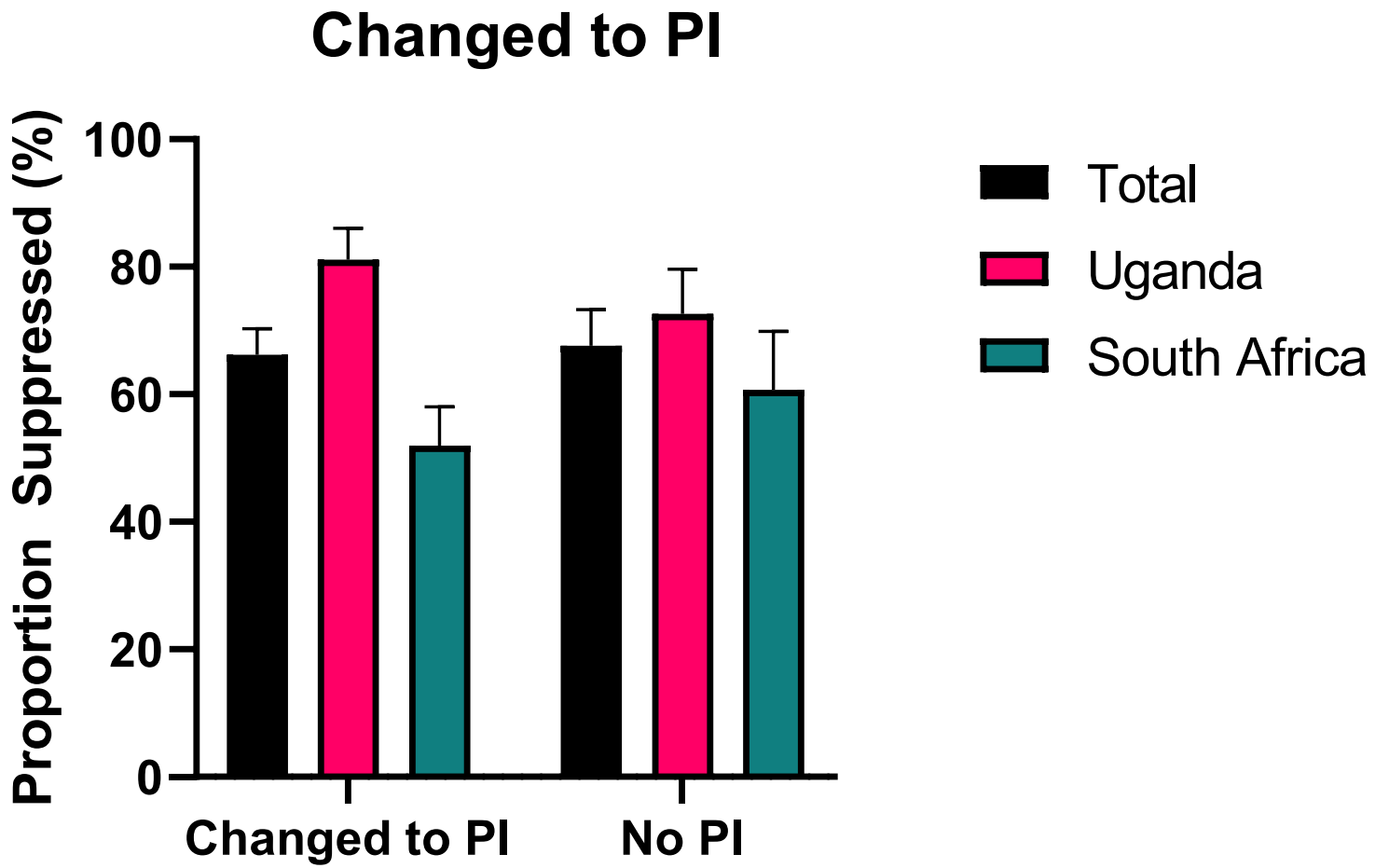


Protease inhibitor use at study endline

	Uganda (n=202)	South Africa (n=260)
Lopinavir/ritonavir	85 (42%)	259 (>99%)
Atazanavir/ritonavir	117 (58%)	1 (<1%)

Unmeasured confounders?

- Poverty/Economic
  - Transportation
  - Food Insecurity
  - Disability Grants
  - Poor social support
- Institutional
  - Long wait times
  - Negative staff experiences
  - Poor health literacy
  - Limited substance abuse treatment and mental health facilities
- Socio-cultural
  - Perceived stigmatization
  - Influence of charismatic churches
  - Traditional healers
  - Gender Inequalities
- Political
  - Migration
  - Controversy over provision of HIV Tx
  - Unfavorable policies

Kagee *J Health Pscyhol*, *Global Public Health* 2010
Western Cape

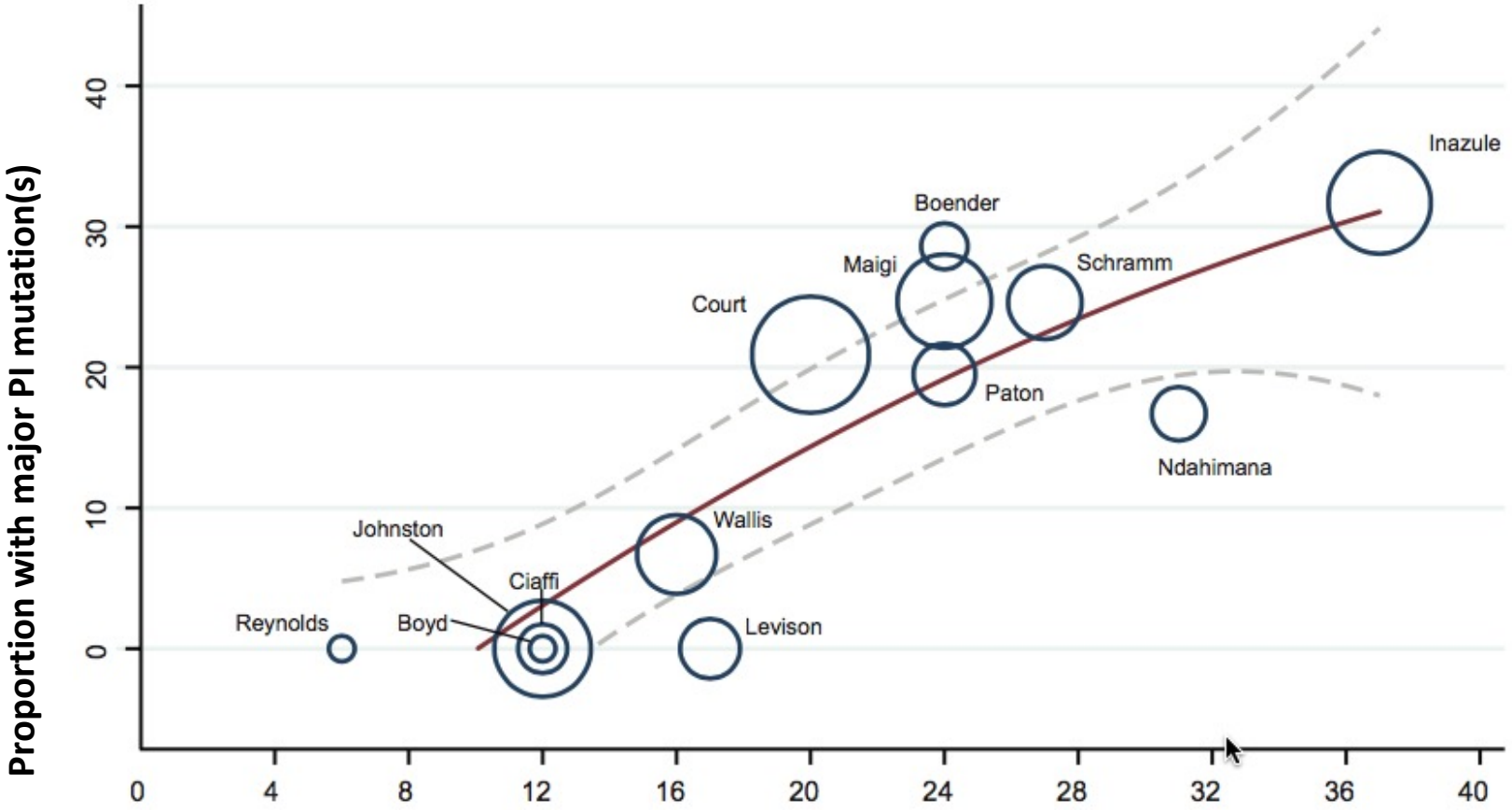
REVAMP trial: Conclusions

- Genotypic resistance testing after first-line failure did *not* improve 9-month virologic suppression rates in Uganda and South Africa
  - Individuals receiving GRT with persistent failure had lower rates of drug resistance at study conclusion
  - Cost-effectiveness analysis forthcoming

- Common predictors of re-suppression were present
  - Older age, higher CD4 count, better adherence
  - Outcomes were substantially better across the board in Uganda
    - Was use of lopinavir/ritonavir partially to blame?

- Interventions that improve management of virologic failure are urgently needed to maintain control of global HIV epidemic

Will PIs and DTG alone save us?



Stockdale et al, CID 2017

Where to next?

- Deep sequencing of viral specimens and pharmacologic testing to determine viral and adherence mediated predictors of failure with and without drug resistance (R01 AI138801, PI: Jonathan Li)

- Urine tenofovir as point of care testing to detect virologic failure and drug resistance (R21 AI145537, PI: Suzanne McCluskey)

- Differentiated models of care to improve management of virologic failure on TLD (R01 under review, PI: Suzanne McCluskey)

In memory of Dr. Bosco Bwana

Acknowledgements

REVAMP Study Team

- Mahomed-Yunus S. Moosa
- Suzanne McCluskey
- Rebecca F. Gilbert
- Selvan Pillay
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- Godfrey Masette
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