Routine 1st-line resistance testing in the current treatment era: **now is not the time**

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- I have no financial disclosures

Key points

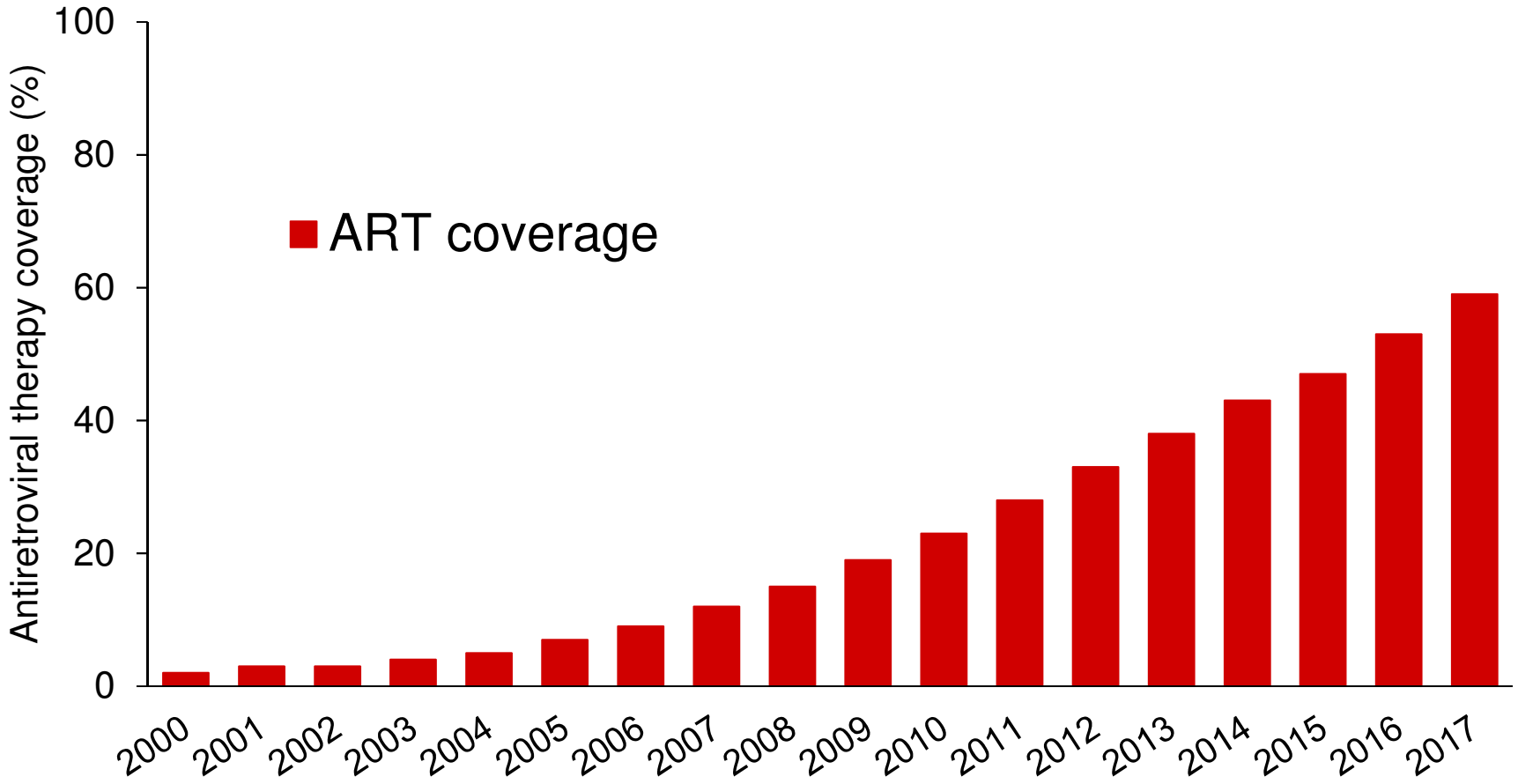
- HIV DR testing can improve clinical outcomes but only after programmatic strengthening
- Rollout of DTG further reduces the benefits of routine HIV DR testing in the general population
- Resources can likely best be used by improving VL monitoring

Global objective

- To optimize the scale-up and sustainability of ART access and viral suppression worldwide to improve life expectancy and decrease transmissions

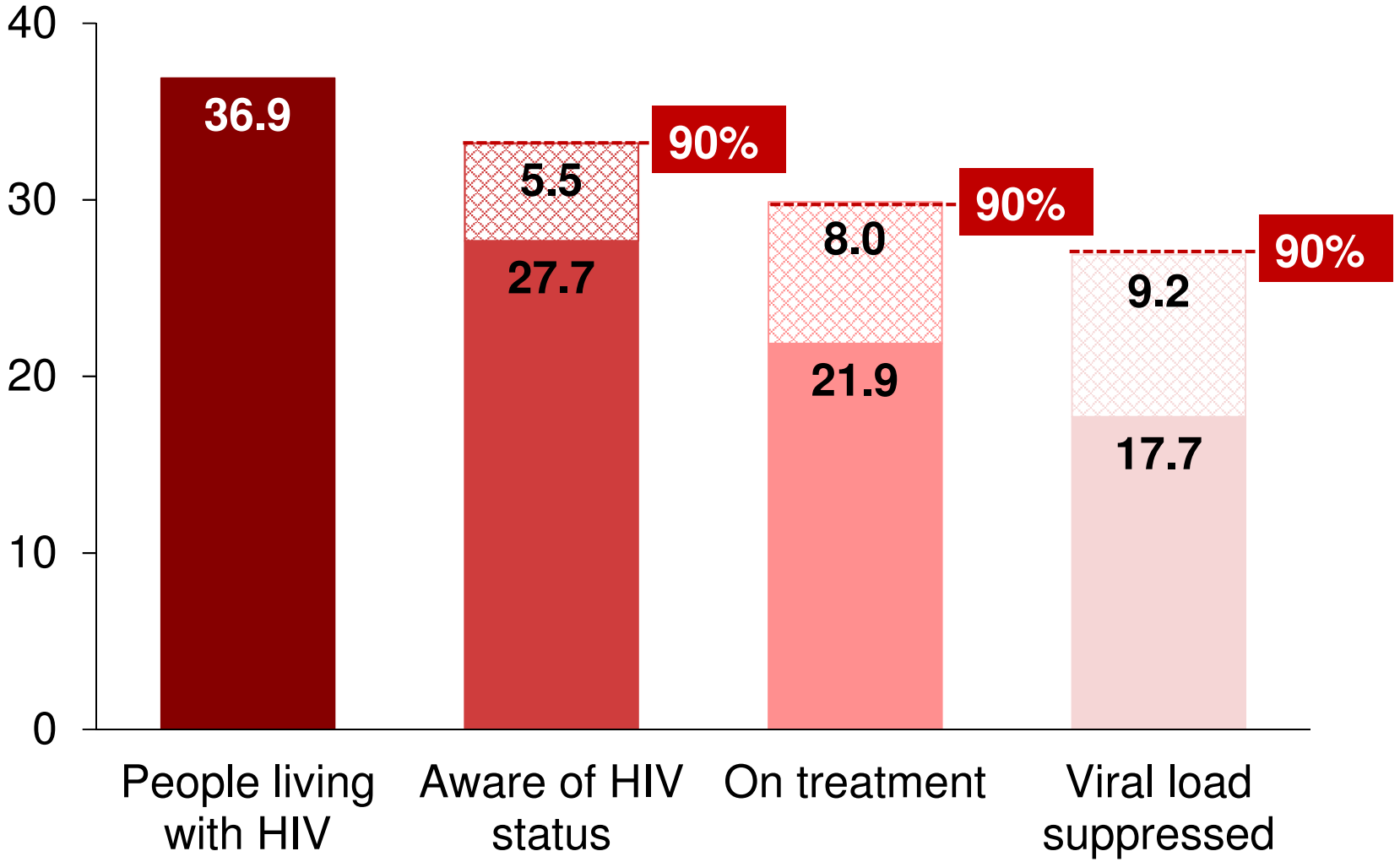
1. Improve ART effectiveness and durability
2. Utilize available resources efficiently

ART scale-up is unprecedented …



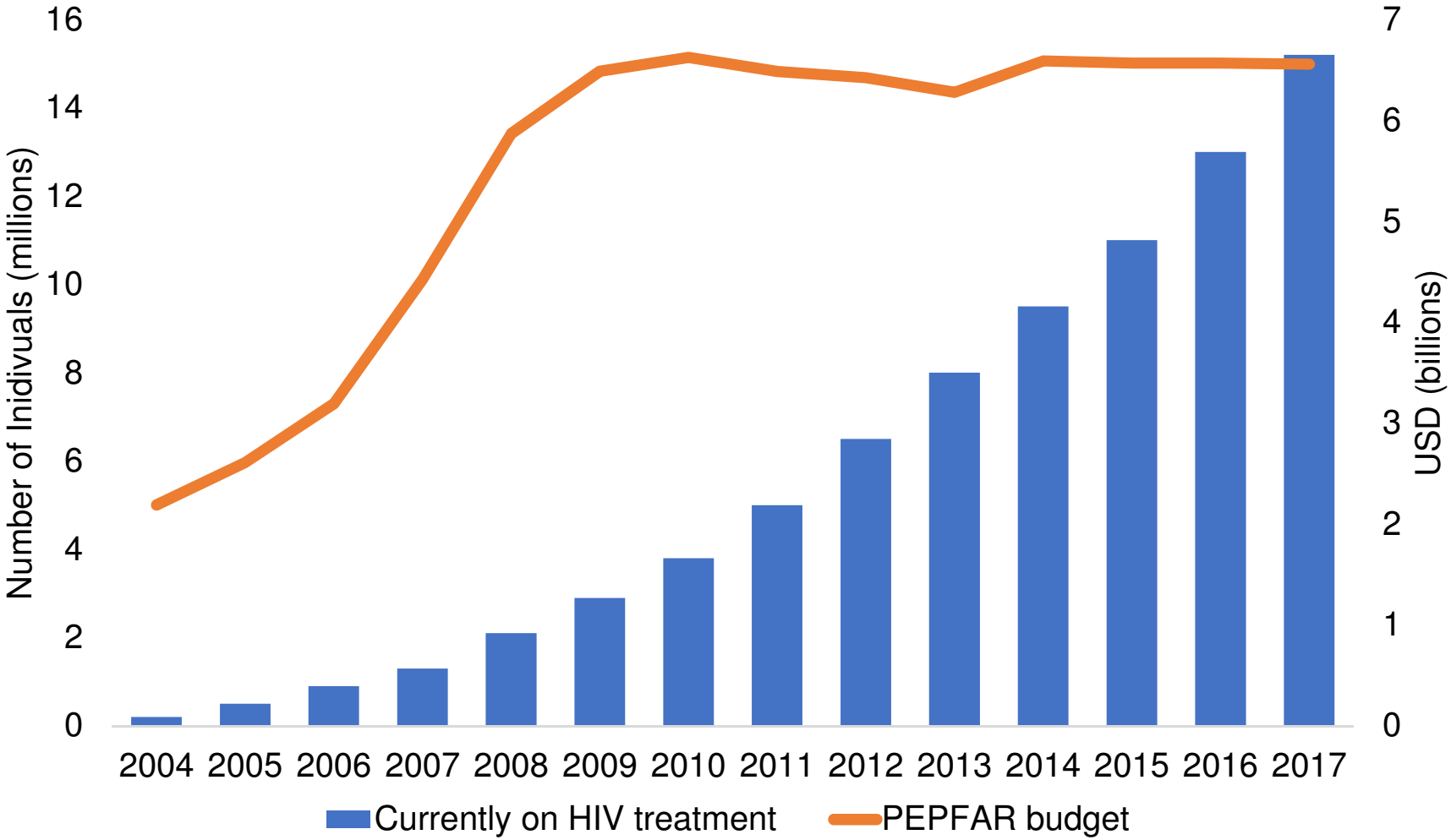
UNAIDS Global AIDS Update 2018

… Ongoing scale-up is still needed



UNAIDS/WHO estimates reported July 2018

Finding efficiencies in HIV care



PEPFAR 2018 Progress Report.

Roadmap

Clinical impact of HIV DR testing

Resource utilization

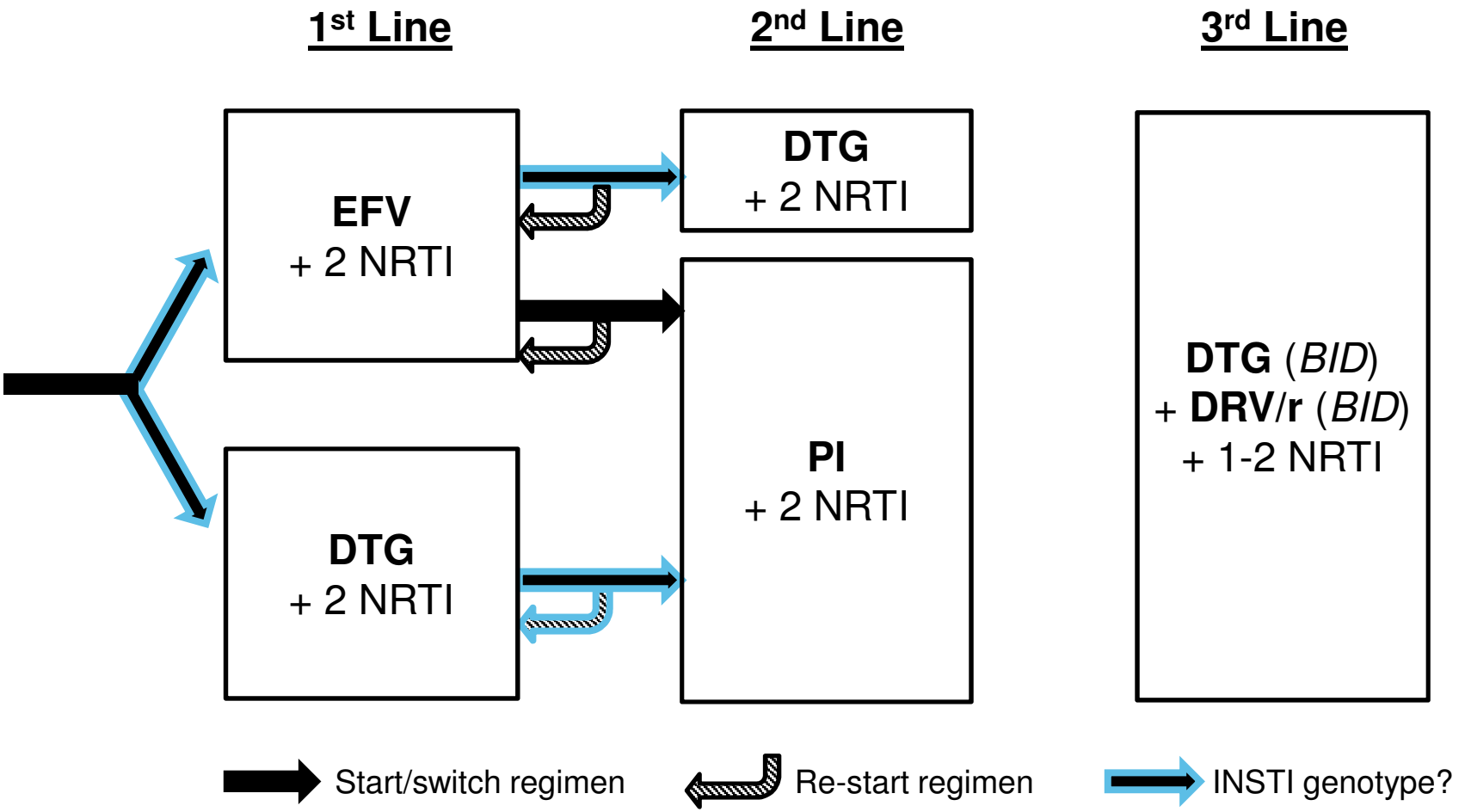
Programmatic challenges

Opportunity costs

Roadmap

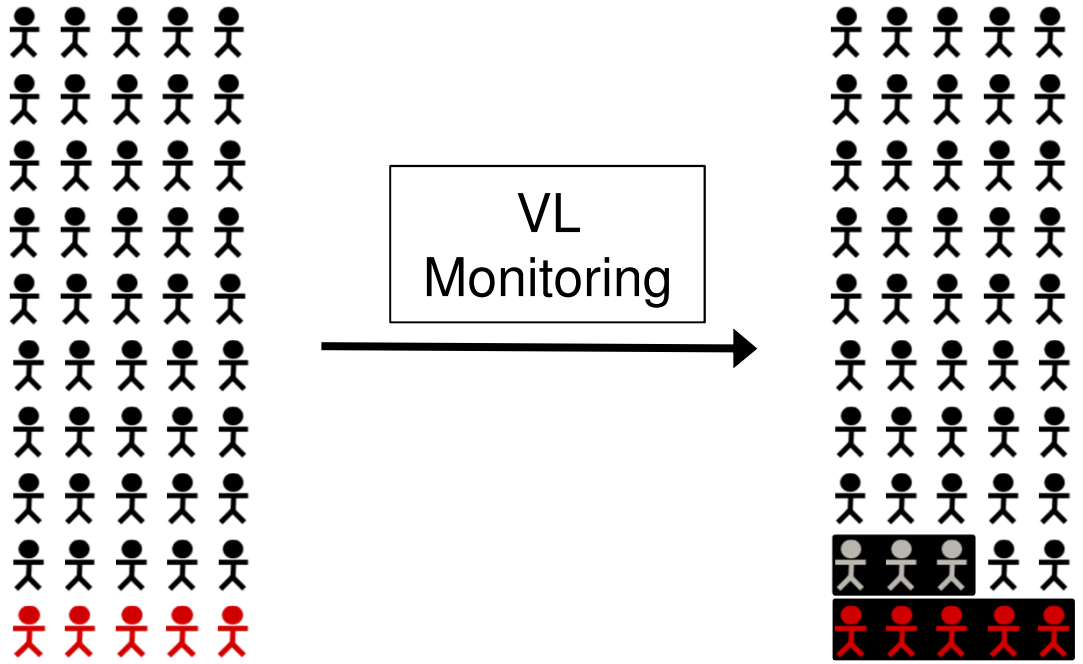
- **Clinical impact of HIV DR testing**
- Resource utilization
- Programmatic challenges
- Opportunity costs

WHO regimen guidelines (July 2018)



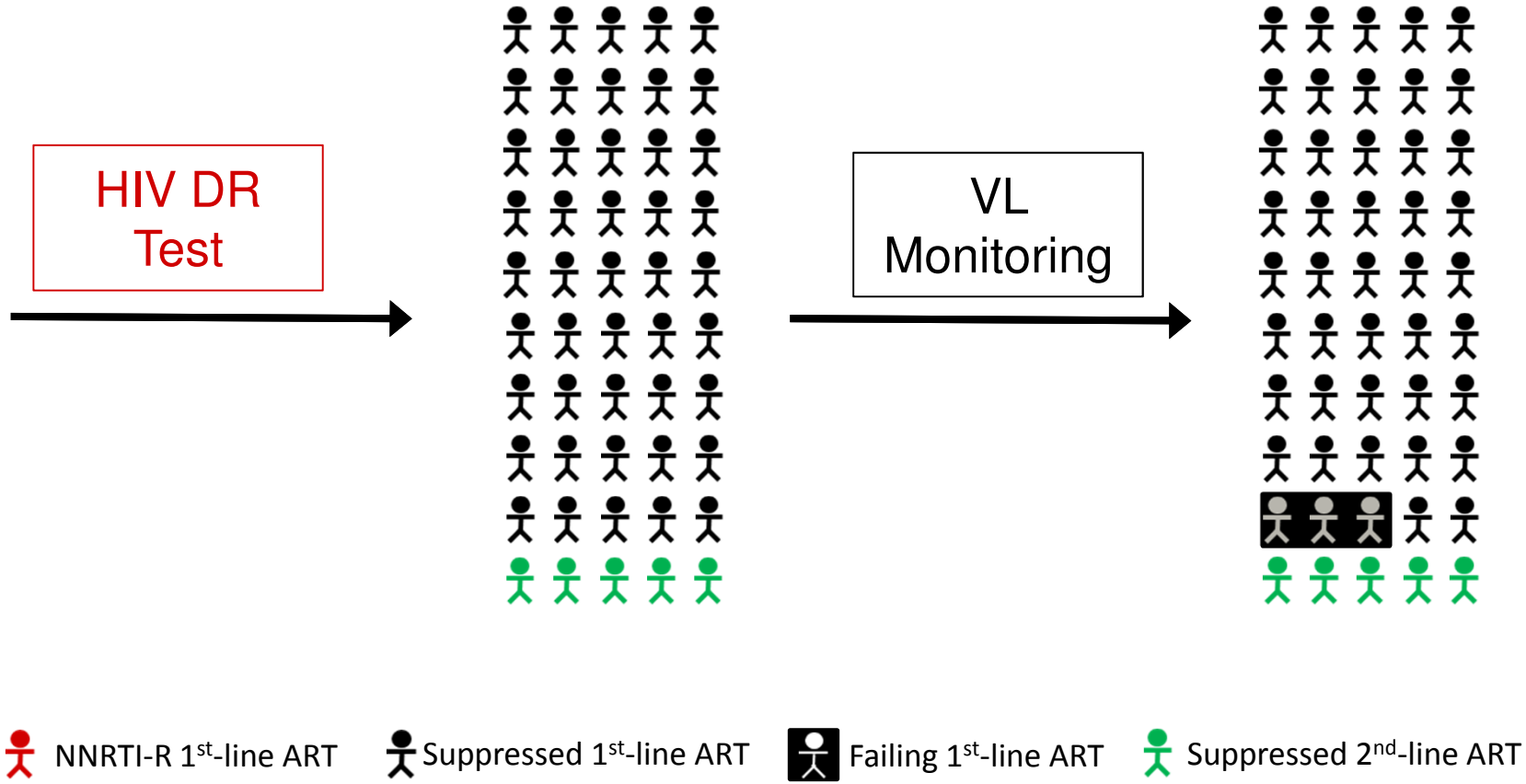
WHO 2018. http://www.who.int/hiv/pub/guidelines/ARV2018update/en/

TLE initiation: no HIV DR testing



NNRTI-R 1st-line ART Suppressed 1st-line ART Failing 1st-line ART

TLE initiation: HIV DR testing

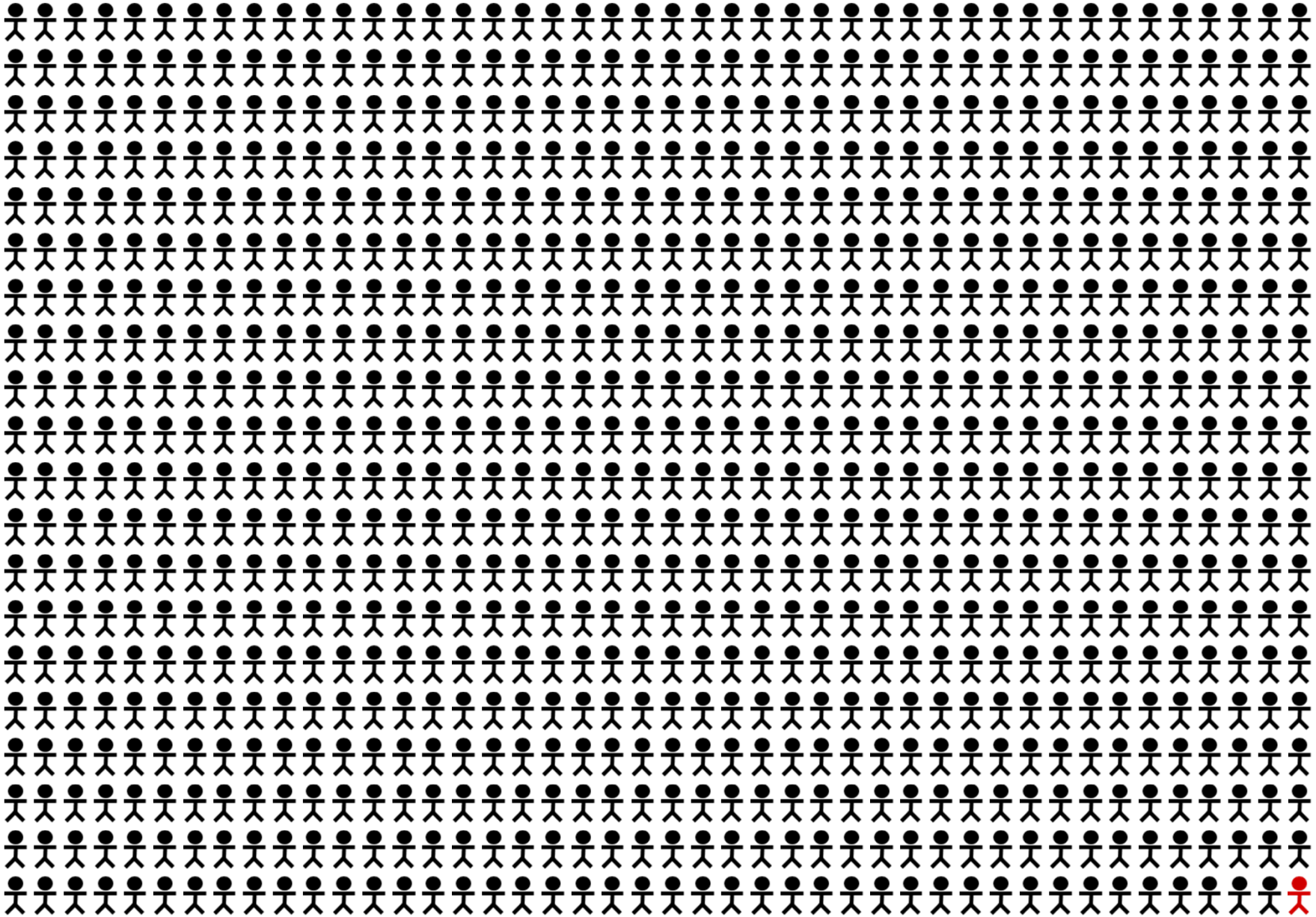


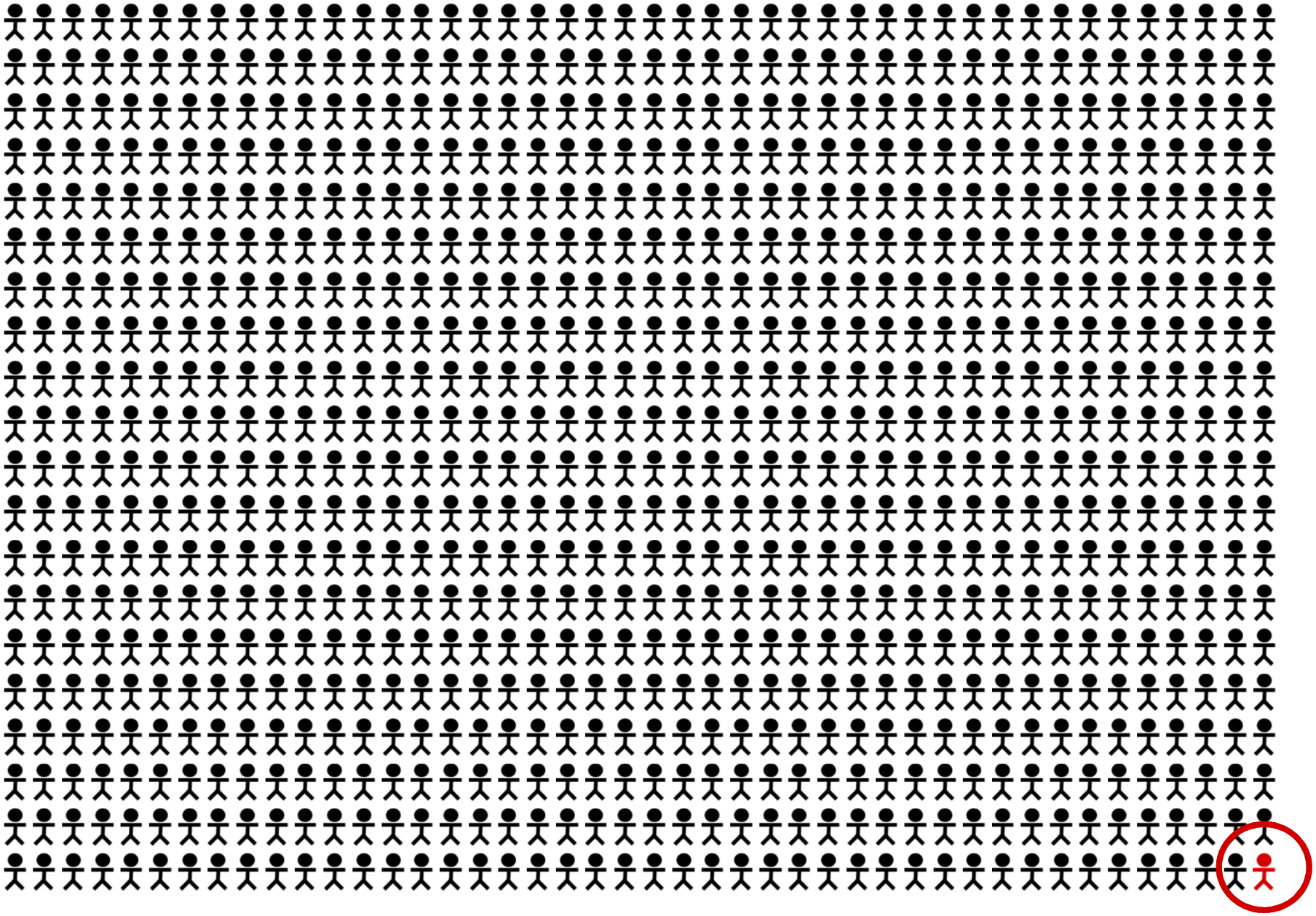
Can NNRTI-R virus suppress with EFV?

- 837 patients initiated TDF/FTC/EFV in rural KZN and had at least 1 VL in follow-up
- Overall, 94.5% suppressed at 12 months

PDR	N=	Time to suppression (months)
No PDR	765 (91%)	3.5
NNRTI-R	67 (9%)	4.1
NRTI/NNRTI-R	5 (<1%)	11.7

Derache and Iwuji *et al*. CID 2018





Transmitted INSTI-R

- Very rare
- Not all INSTI-R mutations have clinical consequences
  - DTG will be active against many INSTI mutations

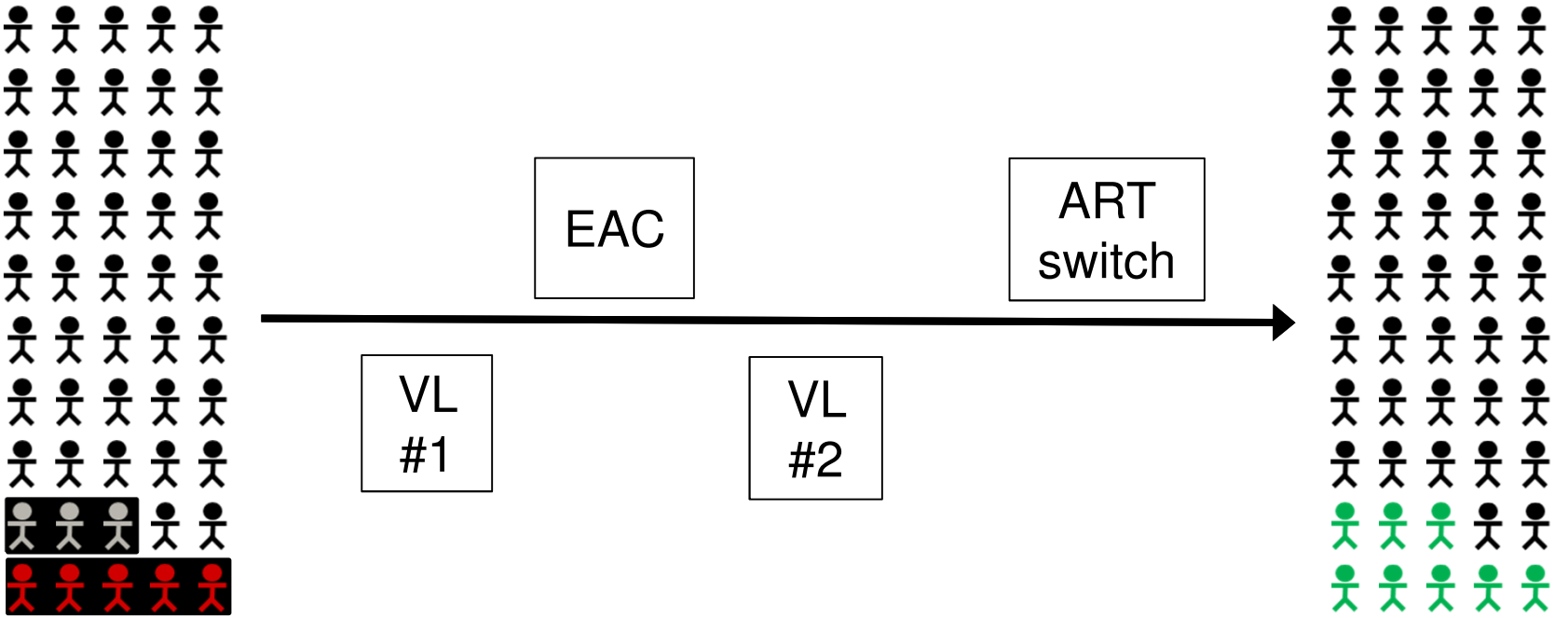
- Koulias *et al.* used simulation modeling to evaluate INSTI-R testing at ART initiation:
  - As long as 20% of transmitted INSTI-R mutations suppressed with DTG, it was not clinically beneficial or cost-effective to test before ART start in the US
  - Assumption: VL monitoring!

Koullias *et al.* CID 2017

HIV DR testing at 1st-line ART initiation

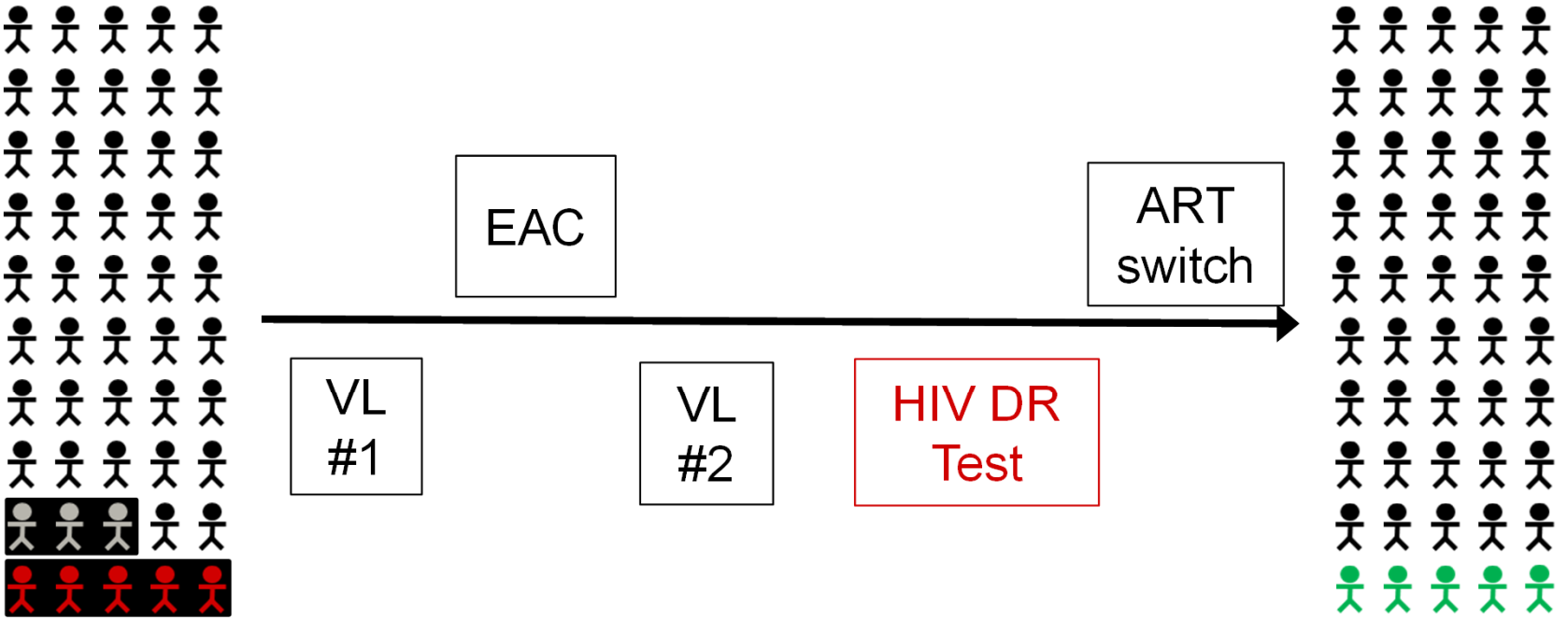
- So many tests!
  - Benefits a small percentage of PWH
  - Insufficient laboratory capacity
  - **Will add delays to ART start for everyone**
- Minimal clinical benefit for patients starting TLD
  - Low PDR
  - Some INSTI mutations will suppress on DTG
- Alternative method to assess for failure
  - VL monitoring
- Costly

TLE failure: no HIV DR testing



NNRTI-R 1st-line ART Suppressed 1st-line ART Failing 1st-line ART Suppressed 2nd-line ART

TLE failure: HIV DR testing



NNRTI-R 1st-line ART Suppressed 1st-line ART Failing 1st-line ART Suppressed 2nd-line ART

Benefits of HIV DR testing

- If susceptible virus:
  - Reduces unnecessary switch to later lines of ART
    - Monthly ART cost will be lower
    - Better tolerated ART regimens
    - Additional lines of ART reserved for future need

- If resistant virus:
  - Prompts appropriate regimen start/switch BUT
    - Genotype results must be interpreted
    - Someone must be empowered to make the switch
    - Next-line ART must be available

CEA: genotype at 1st-line ART failure

	Country	Life expectancy	Cost	Conclusion
Rosen 2011	South Africa	NA	--	**Cost-neutral**
Levison 2013	South Africa	↑	↑	**Cost-effective** ($900/YLS)
Phillips 2014	Zimbabwe	↑	↑	**Not cost-effective**

CEA: genotype at failure

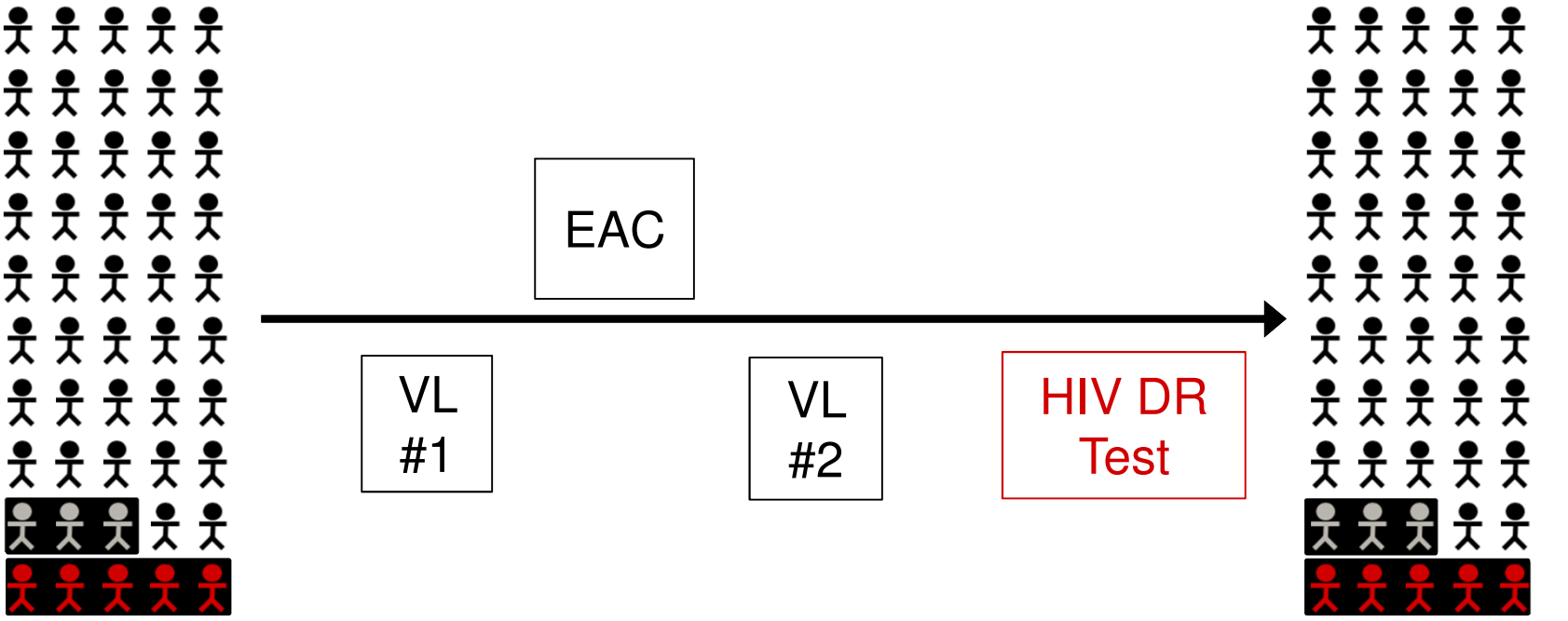
- No analyses published regarding genotype after failure on INSTI regimen

- Genotype testing was cost-neutral or CE
  - ~80% of patients fail ART with resistant virus
  - Unnecessary switches are costly bc 2nd-line ART is 2-5x more expensive than 1st-line ART
  - HIV DR testing prompts *appropriate* switches but must not create delays (Not CE if >5 months)

- HIV DR testing not CE
  - Benefits of PI-based ART for poorly adherent
  - Not all switch to 2nd-line, even with HIV DR test

Rosen *et al.* JIAS 2011; Levison *et al.* CID 2013 Phillips *et al.* Lancet HIV 2014.

TLE failure: HIV DR testing – reality?



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HIV DR testing doesn't solve inaction

- Why do patients fail 1st-line ART for prolonged periods of time?
  - Virologic failure goes unrecognized
  - Clinicians do not recommend 2nd-line despite VF
  - 2nd-line is not available (stockouts)

HIV DR testing doesn't solve inaction

- Why do patient fail 1st-line ART for prolonged periods of time?
  - Virologic failure goes unrecognized
    - **Improve VL monitoring**
  - Clinicians do not recommend 2nd-line despite VF
    - **Empower clinicians to advocate for 2nd-line ART after repeat VL remains detectable**
  - 2nd-line is not available (stockouts)
    - **Improve supply chains**

Roadmap

Clinical impact of HIV DR testing

Resource utilization

Programmatic challenges

Opportunity costs

Test costs

- Usually described as “$XX/test”
- Such estimates rarely include many of the important contributors to what it takes to deploy a diagnostic test

Resource utilization

- Laboratory infrastructure
  - Capital costs
  - Maintenance costs
- Fixed versus marginal costs
  - Fixed: for test availability (machine, staff salaries, QC)
  - Marginal: per test (reagents, staff time)
- Additional costs
  - Transport of specimens
  - Communication of results with care providers

Resource utilization ≠ per test costs

Cost component of POC-CD4	Mobile clinic	Clinic
Cost for QC materials ($/day)	$0.43	$0.43
Machine start up (hours/day)	0.5	0.5
Salary ($/hour)	$14.67	$8.82
Salary cost for QC ($/day)	$7.33	$4.41
Total cost for QC ($/day)	**$7.76**	**$4.84**

Adapted from Larson et al. PLoS One. 2012

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Anticipated challenges with DR testing

- New algorithm needed for providers
  - Who will be trained to interpret genotype results?
  - Who will be empowered to switch regimens?

- Avoid re-centralization
- Do not divert resources from VL scale-up
- Ensure accessibility and affordability of 2nd-line

- Given challenges surrounding DTG, now is not the time to add program complexity

Roadmap

Clinical impact of HIV DR testing

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Opportunity costs

- What will not be funded if routine HIV DR testing is started?
- Would scale-up of VL monitoring slow?
  - Only 10% of focus countries report ≥90% of PWH on ART with annual VL
- Would ART availability be compromised?
  - 48% of focus countries reported ART stock outs in past year

Future steps

- Ongoing improvement in programmatic flow
  - Consistent viral load monitoring
  - Increased switch to 2nd-line for patients failing 1st-line
  - Reduce stock outs
- Special populations
  - Children
- Surveillance ≠ clinical decision-making
  - Further drug resistance data collected now to inform future guidelines
- Hope for the best, but anticipate the worst
  - Now is the time to develop a plan; simulation modeling can provide estimates and project outcomes

Key points

- HIV DR testing can improve clinical outcomes but only after programmatic strengthening
- Rollout of DTG further reduces the benefits of routine HIV DR testing in the general population
- Resources can likely best be used by improving VL monitoring

Thank You

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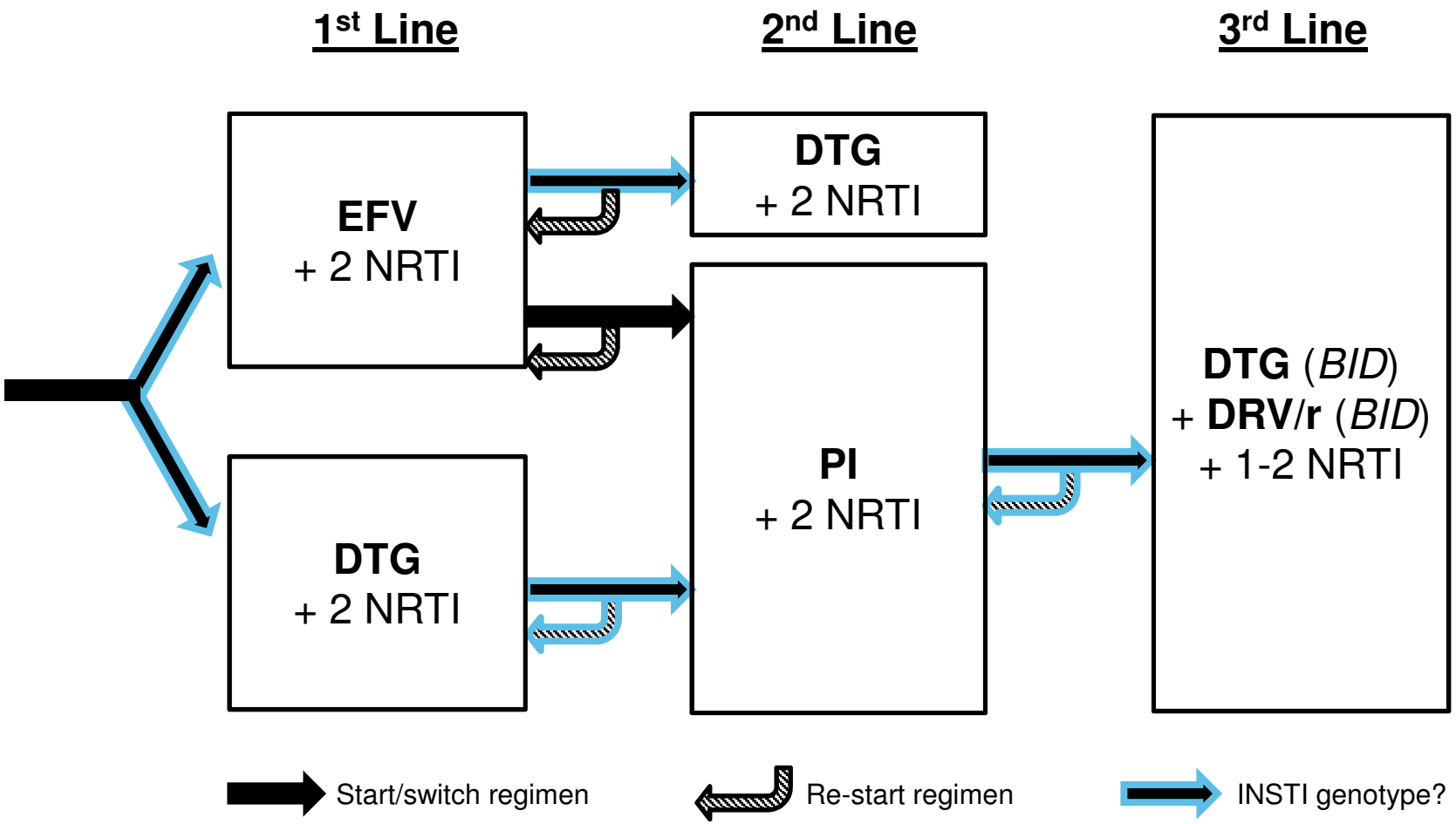
SUPPLEMENTARY SLIDES

WHO regimen guidelines (July 2018)



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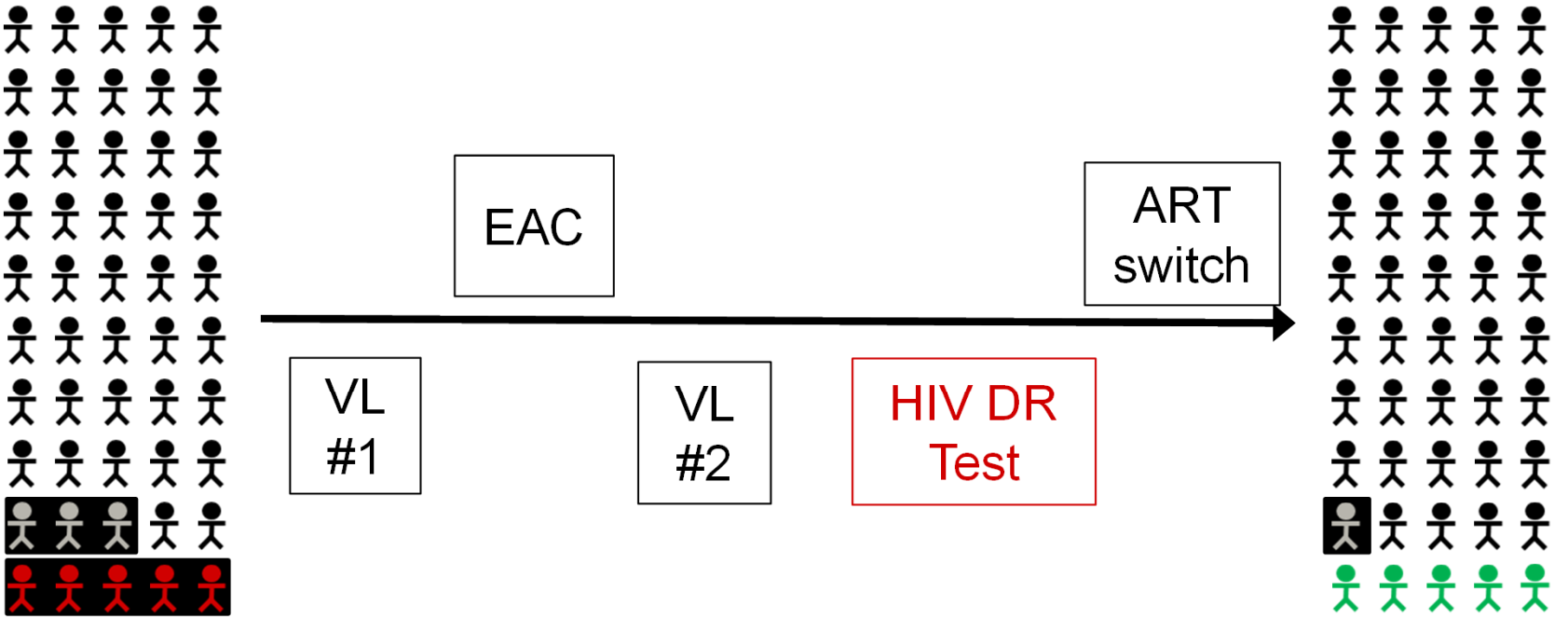
TLE Failure: HIV DR Testing



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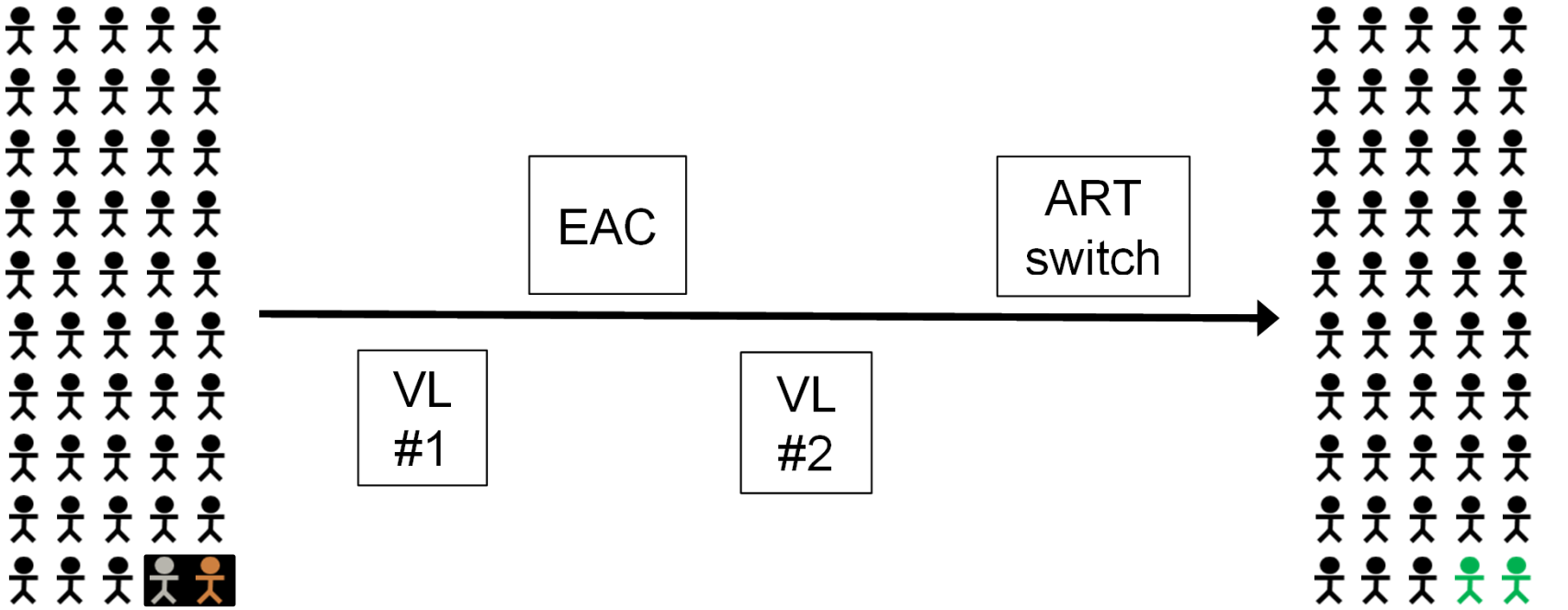
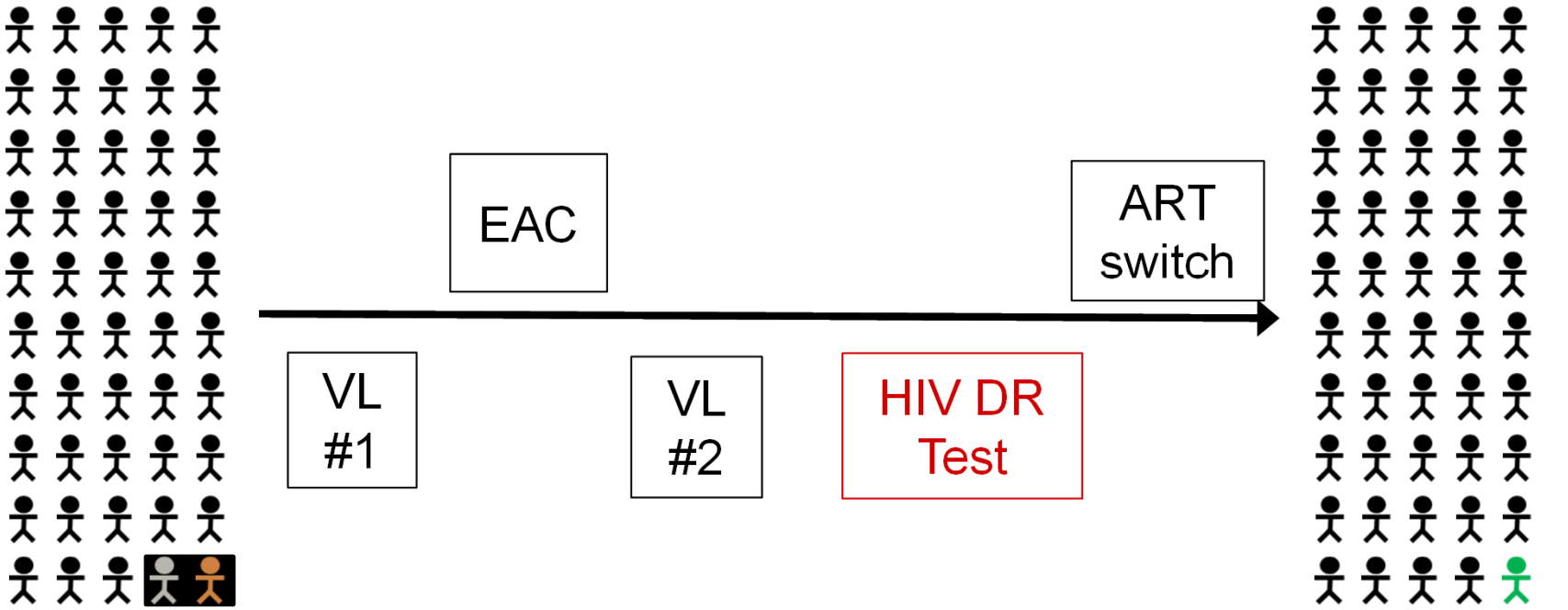


INSTI-R 1st-line ART Suppressed 1st-line ART Failing 1st-line ART Suppressed 2nd-line ART

LM8

TLD Failure: HIV DR Testing



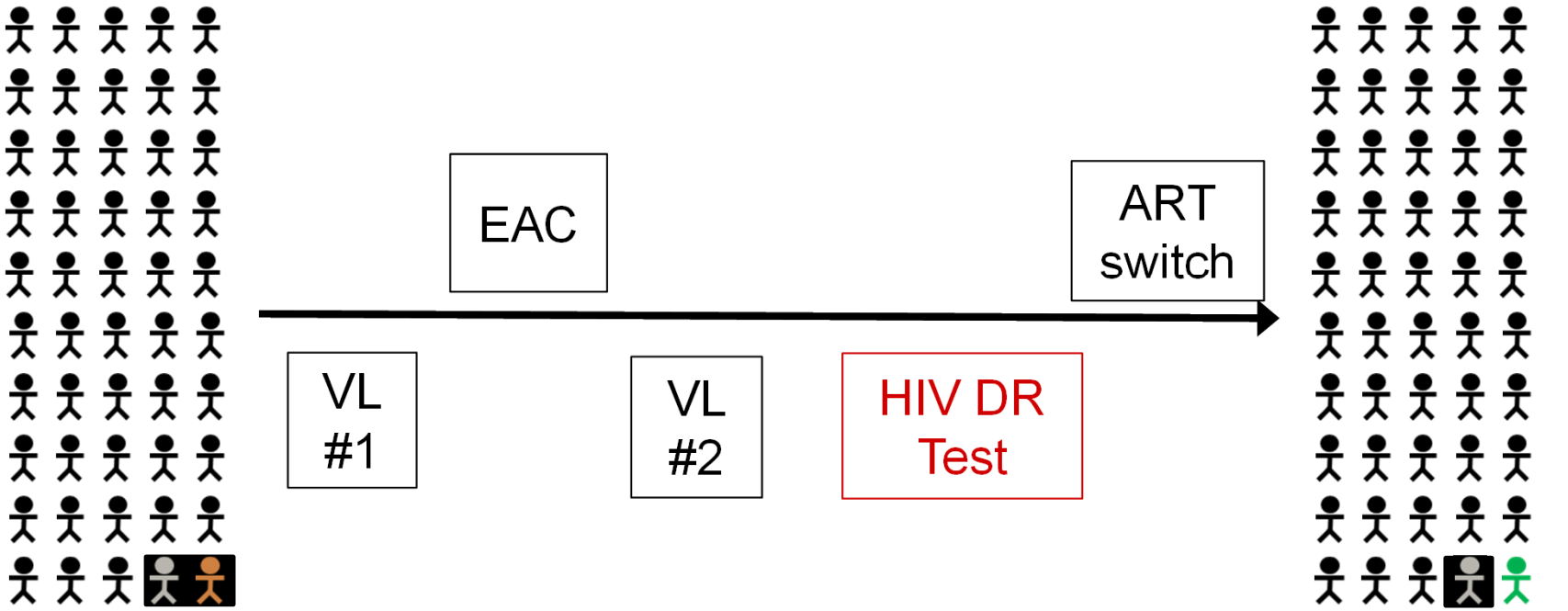
INSTI-R 1st-line ART Suppressed 1st-line ART Failing 1st-line ART Suppressed 2nd-line ART

LM8 Option #1

Lucia Millham, 2018/10/22

LM9

TLD Failure: HIV DR Testing



INSTI-R 1st-line ART Suppressed 1st-line ART Failing 1st-line ART Suppressed 2nd-line ART

LM9 Option #2

Lucia Millham, 2018/10/22

Clinical Decision-Making

	ART Initiation	ART Switch
TLE	TLD	TLD
TLD	?	PI-based ART

** NRTI resistance pattern used to determine NRTI pair

Data Are on the Horizon

Inclusion criteria: patients failing NNRTI + 2NRTI

Study	Intervention	Status
DAWNING	DTG vs LPV/r	Awaiting final data
D2EFT	DRV/r + 2NRTI DTG + TDF/XTC DRV/r + DTG	Enrolling
NADIA	DTG vs DRV/r + TDF/XTC vs AZT/3TC	Protocol finalization

Adapted from ClinicalTrials.gov

VL Monitoring is Essential

- Among PWH who have close follow-up with VL testing to assess response to ART, HIV DR testing
  - Reduce transmissions
  - Prompt adherence counseling
  - Trigger resistance testing or empiric ART switch

Clinical benefits of HIV DR testing

- Pretest probability of resistance:
  - Prevalence of pretreatment drug resistance
  - Likelihood of developing acquired drug resistance
    - Genetic barrier to resistance
    - Tolerability of regimens (adherence)
    - Frequency of stockouts

- Selection of optimal ART regimen
  - Depending on HIV DR test result