Consultation on Global Trends of HIV Drug Resistance
Rockville, Maryland, USA
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Use of modelling to inform policy on responding to potential future high levels of pre-treatment drug resistance

Andrew Phillips

and the Working Group on Modelling Potential Responses to High Levels of pre-ART Drug Resistance in Sub-Saharan Africa

UCL

Background

- WHO recommends pre-treatment drug resistance surveys in populations initiating ART, but these are not often prioritised by countries.

- Where surveys are done, it is important to consider options for countries if high levels of pre-ART NNRTI resistance are identified.

Objectives

To use modelling to evaluate:

- the potential for unidentified sub-epidemics of high levels of transmitted HIV drug resistance in sub-Saharan Africa
- the cost effectiveness of policy options in the presence of a given level of pre-ART NNRTI resistance

Modelling approach

- Individual-based simulation model of HIV transmission, effect of ART, considering specific drugs and resistance mutations*
- Model based around southern Africa with multiple potential ***setting scenarios*** generated through simulation
  - Each run of the model program generates a scenario for a population of ~35,000 adults
- Parameters varied randomly within plausible bounds for settings in the region include:
  - ART adherence profile and interruption rate
  - ART monitoring strategy (whether viral load used)
  - Switch rate after first line failure
- We consider setting scenarios in which the level of pre-ART drug resistance in ART naïve initiators is below 15% in 2014

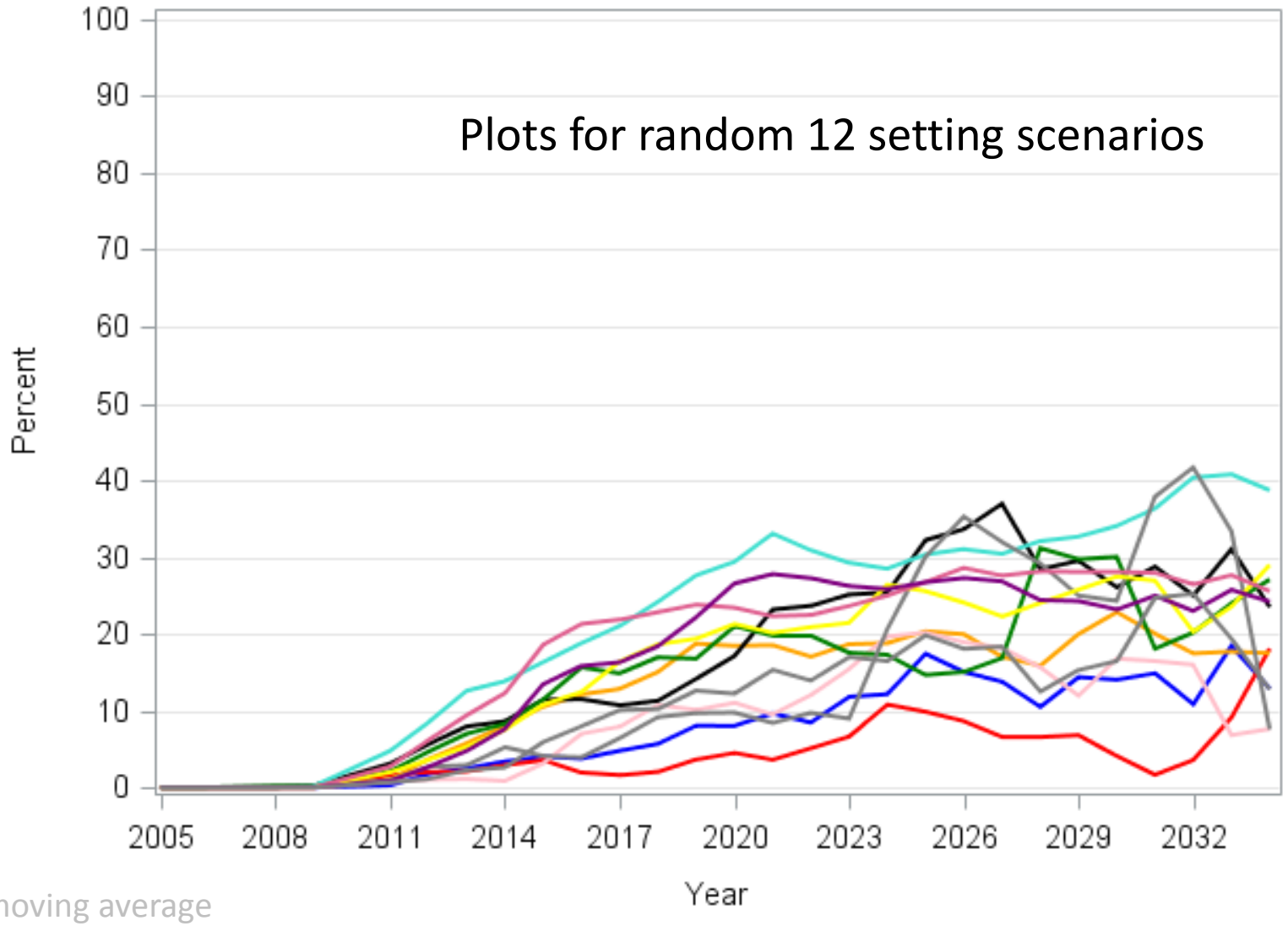
**Phillips et al 2011, Cambiano et al 2013, Nakagawa et al 2012*

Characteristics of setting scenarios in 2015

Distribution of HIV epidemic and programmatic characteristics across > 2000 setting scenarios. People age 15-64.

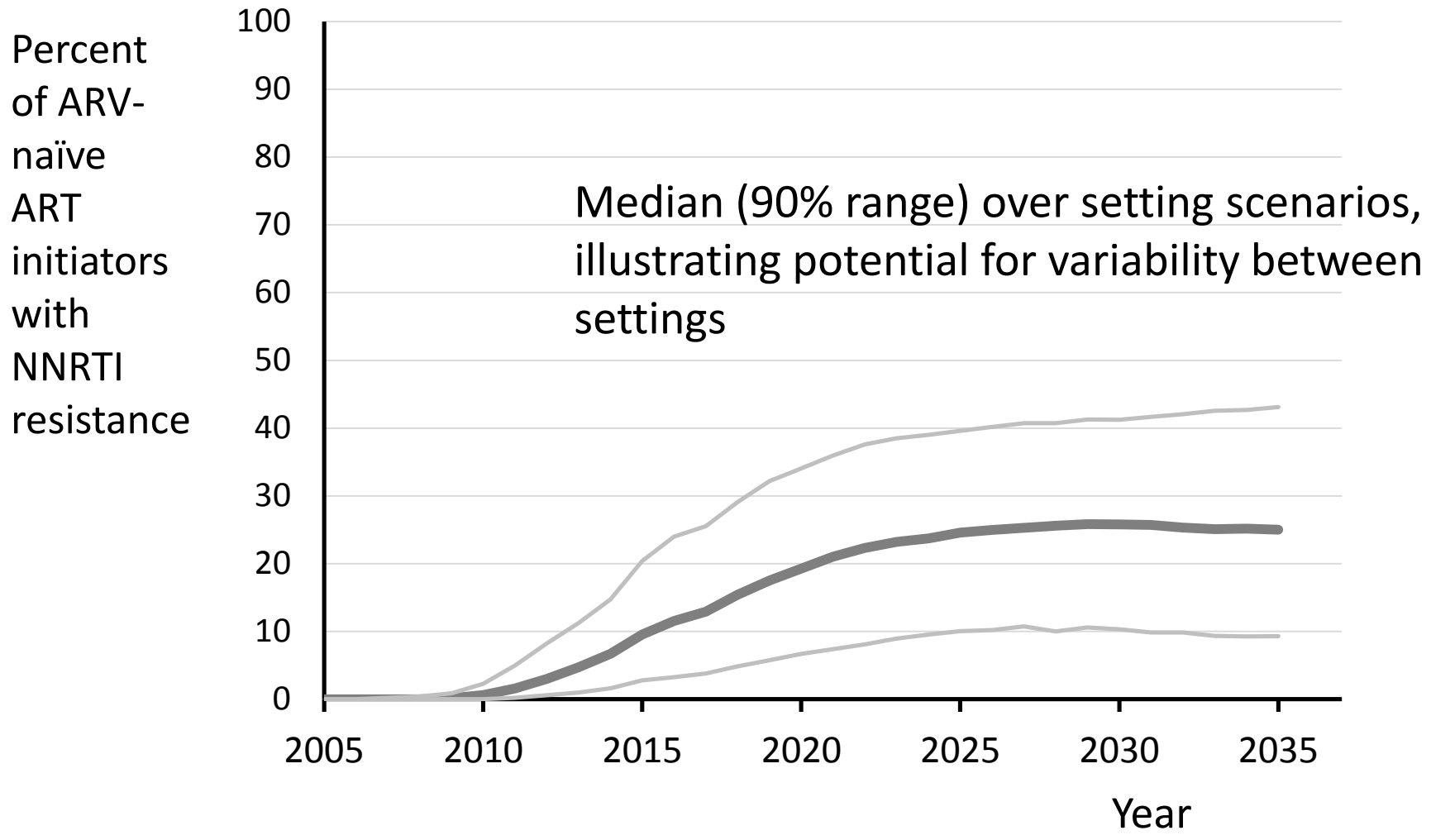
	Median; 90% range
HIV prevalence	8% (5% - 17%)
Proportion of all HIV positive people on ART	62% (44% - 76%)
Of ART initiators without prior ARV exposure, % with NNRTI resistance (i.e. TDR)	
in majority virus	9% (2% - 20%)
in minority or majority virus	9% (2% - 21%)
Of ART initiators with prior ARV exposure, % with NNRTI resistance	
in majority virus	16% (5% - 34%)
in minority or majority virus	20% (7% - 41%)
% of ART initiators with prior ARV exposure	20% (9% - 34%)

Modelled trend in % of ARV-naïve initiators with transmitted NNRTI drug resistance, with no programmatic changes



3 year moving average

Modelled trend in % of ARV-naïve initiators with transmitted NNRTI drug resistance, with no programmatic changes



3 year moving average

Objectives

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Policy options considered

- No change
- For all ART initiators: dolutegravir first line regimen
- For all ART initiators and all on first-line ART: move from efavirenz to dolutegravir
- For all on first-line ART: increase the rate of switching to 2nd-line ART in people with first line failure (from 0.05-0.20 to 0.5 / 3 months)

A fuller range of policy options initially considered – including individual-based resistance testing - these above were found to be the leading contenders

Modelling approach

- For each setting scenario, consider the situation in 2016 when there is a certain level of drug resistance in ART initiators and compare outcomes of potential policy options over the next 20 years.

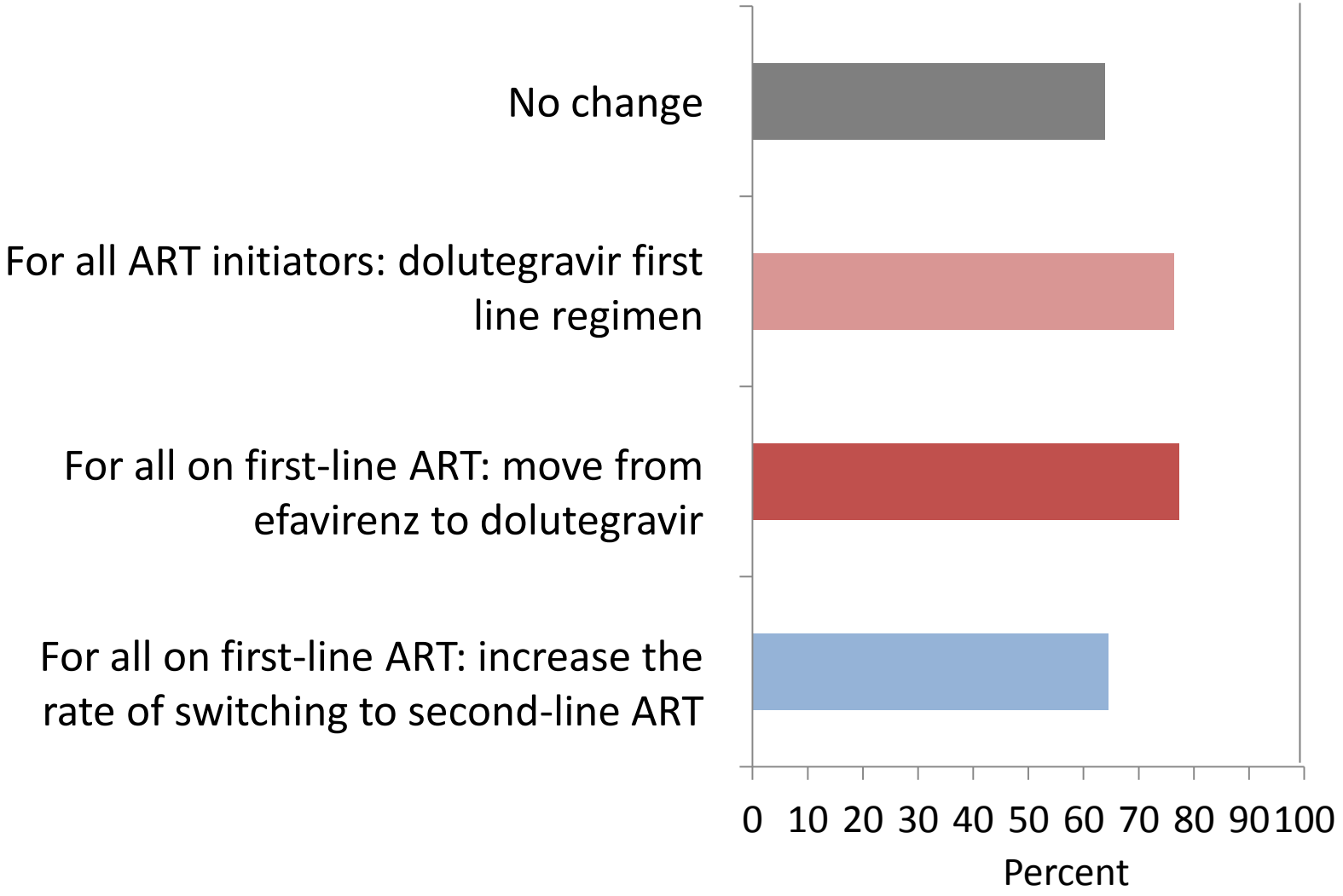
- Assumptions on effectiveness of dolutegravir vs efavirenz

  - lower rate of resistance
  - greater tolerability

**Single trial. Walmsley et al 2013 and 2015*

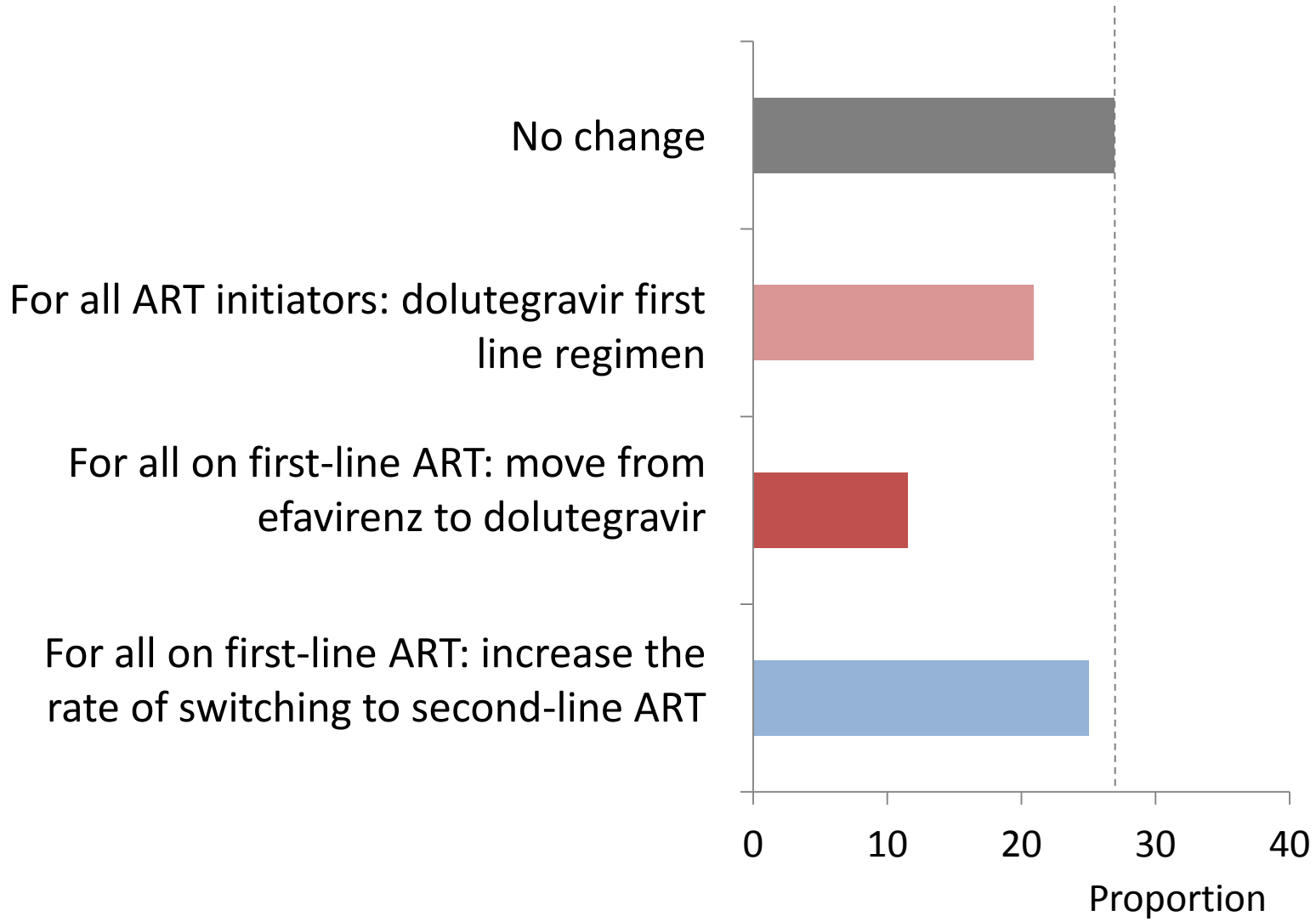
Mean percent with viral load < 1000 cps/mL 1 year from ART initiation 2016 - 2036

Restricting to setting scenarios where > 10% of ART initiators have NNRTI resistance in 2016



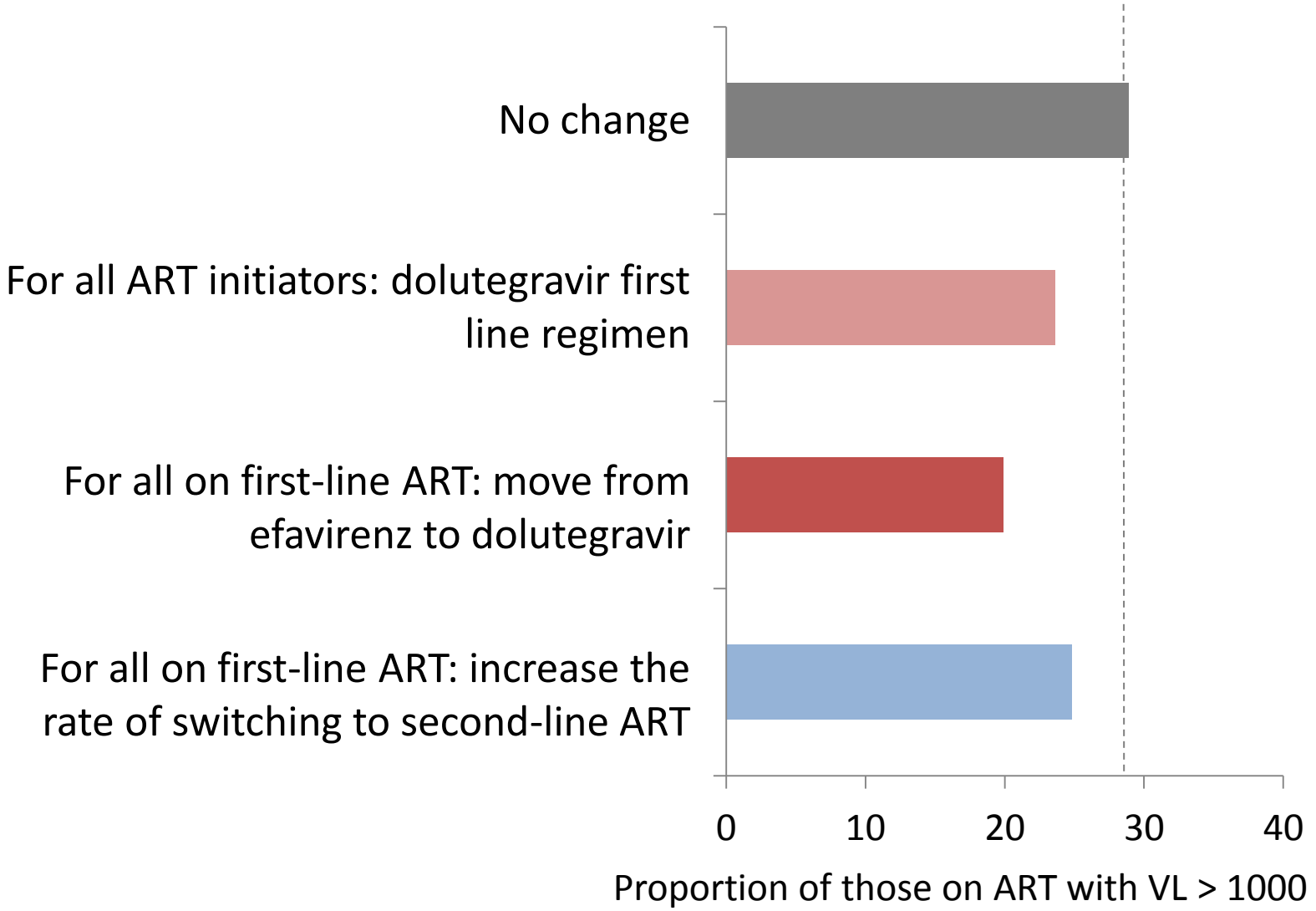
Mean proportion of ART-naïve initiators with NNRTI resistance 2016 - 2036

Restricting to setting scenarios where > 10% of ART initiators have NNRTI resistance in 2016



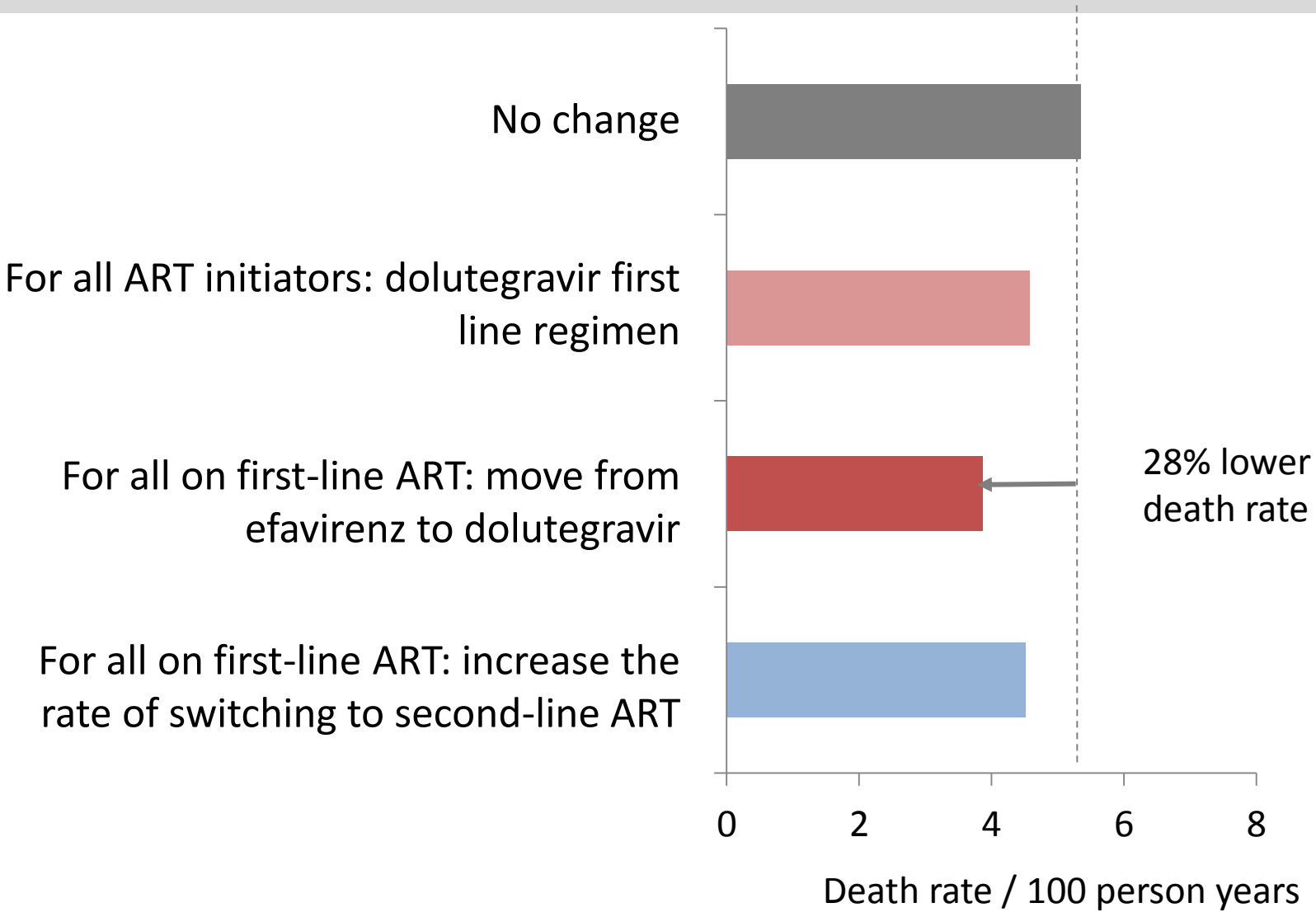
Mean proportion of people on ART who are virologically failing (viral load > 1000 cps/mL) 2016 - 2036

Restricting to setting scenarios where > 10% of ART initiators have NNRTI resistance in 2016



Mean death rate in people on ART 2016 - 2036

Restricting to setting scenarios where > 10% of ART initiators have NNRTI resistance in 2016

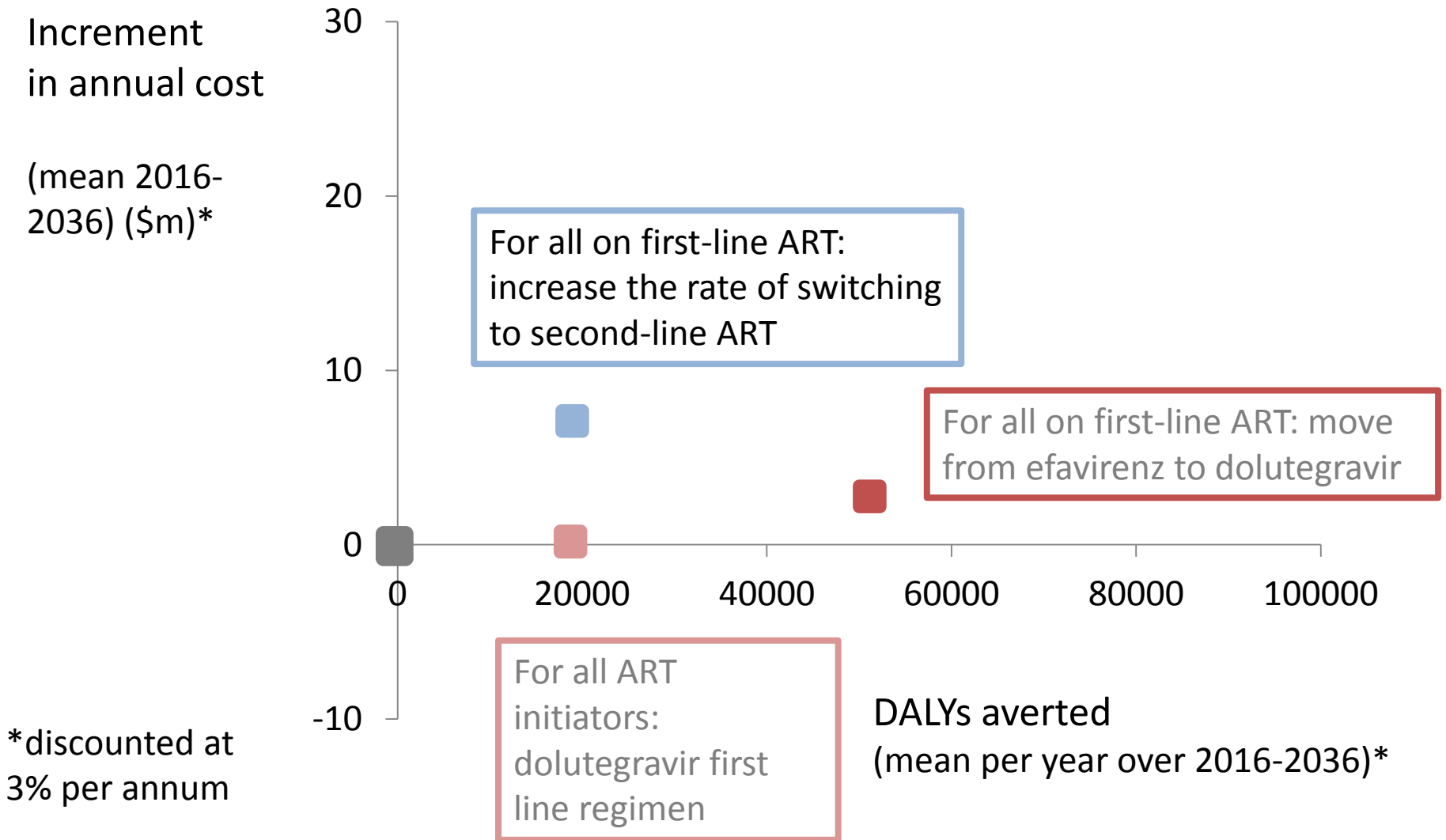


Unit costs

efavirenz + 3TC + tenofovir (per year)	$120*
dolutegravir + 3TC + tenofovir (per year)	$126* ($44 dolutegravir)
atazanavir/r + 3TC + zidovudine (per year)	$260*
CD4 count	$10***
viral load	$22****
clinic/programme costs (per person per year)	$80 ($40 if viral load < 1000)+
adherence intervention when VL > 1000	$10**
switching to 2nd line (non-drug costs)	$20**
average cost for treating:	
WHO stage 4 condition	$200**
WHO stage 3 condition	$20**
TB	$100**
country transition of first line regimen	$100,000

** MSF Untangling the Web 2015, Global Fund procurement figures; CHAI announcement Jan 16; ** assumptions; *** Hyle et al; PLOS Med 2014 *** MSF costing study, Global Fund procurement figures; + Tagar et al 2014; viral load informed differentiated care, Nature 2015*

Increment in cost and DALYs averted relative to no change in policy if **> 10%** of all ART initiators have NNRTI resistance in 2016



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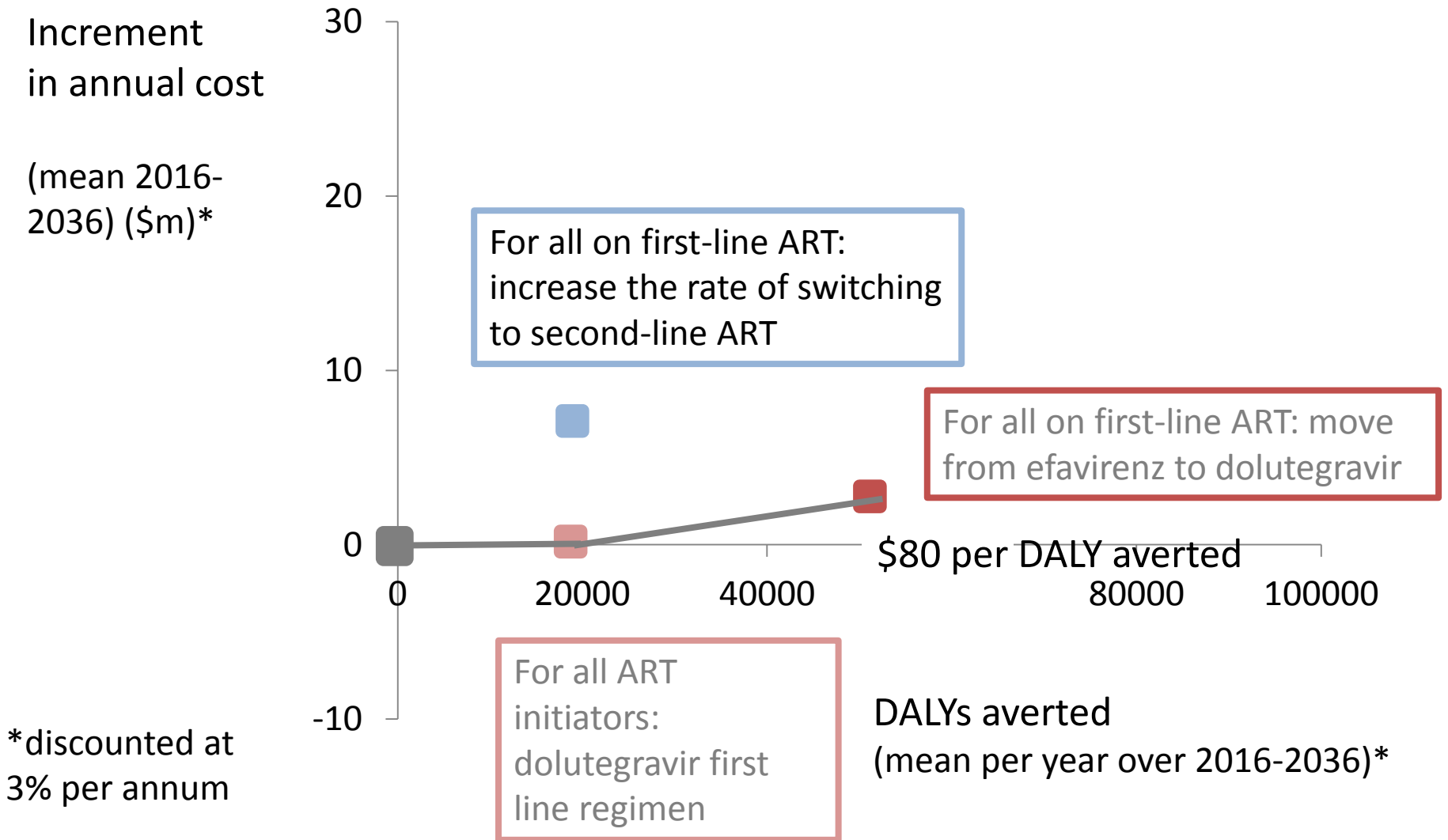
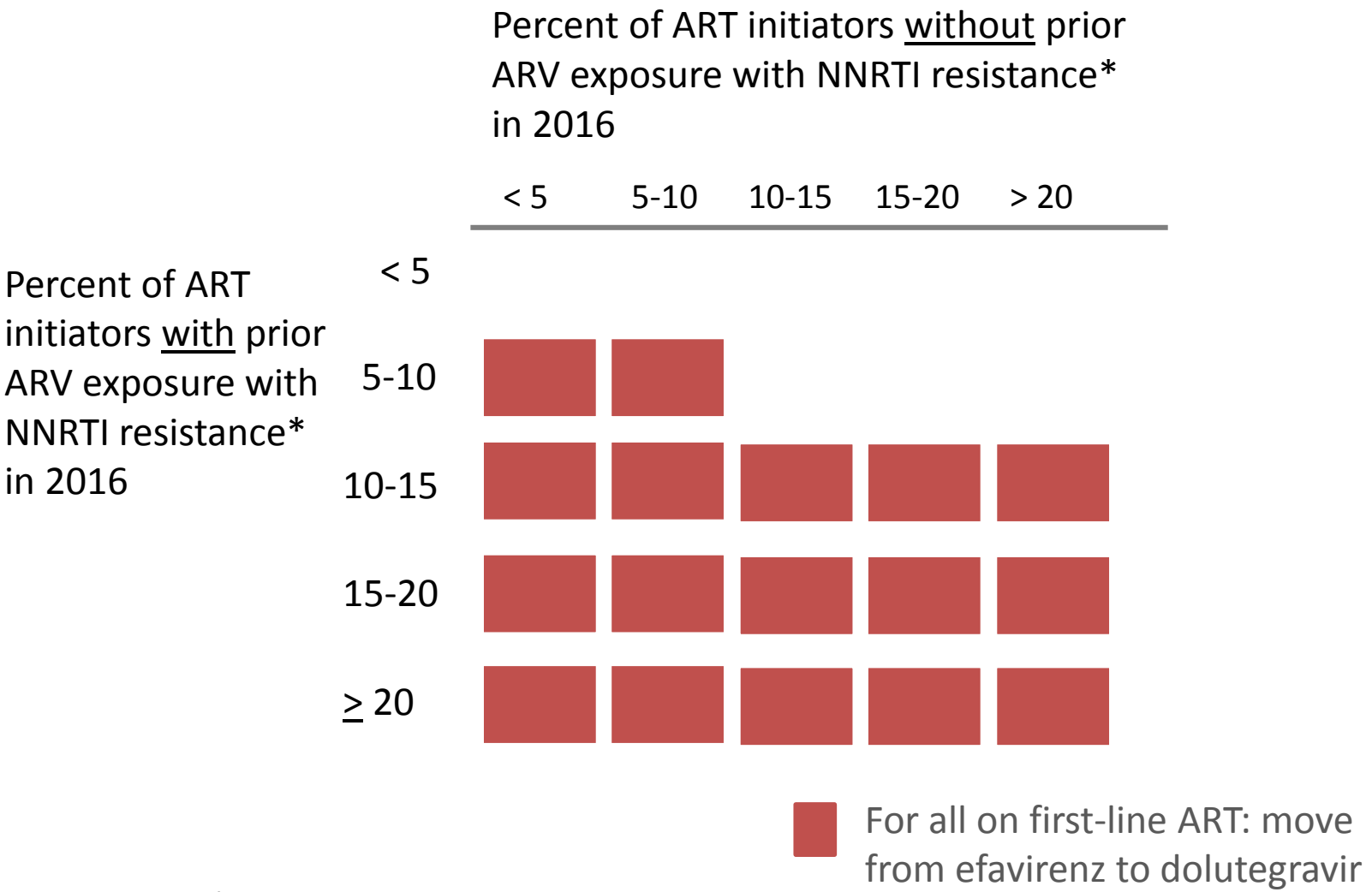


Most cost-effective policy according to results from pre-treatment drug resistance surveys



* In majority virus $500 cost effectiveness threshold

Comments

- High levels of pre-treatment drug resistance should prompt review of program quality.

  Even so, once transmitted drug resistance is present this will undermine the response to first line ART even if improvements are then made.

- Further sensitivity analyses:
  - higher rates of toxicity with dolutegravir
  - higher costs of dolutegravir and of transition process

- We focussed on low income settings in sub-Saharan Africa – elsewhere generic dolutegravir is not available.

Conclusions – Monitoring of Drug Resistance

- Without monitoring of pre-ART NNRTI drug resistance, there is potential for undetected development of extremely high levels of transmitted drug resistance in some settings, making first line ART ineffective in a substantial proportion of people.

- There is potential for rapid changes in levels of transmitted drug resistance so monitoring at least every 3 years seems appropriate.

Conclusions – Response to High Levels of Drug Resistance

- A future transition from efavirenz to dolutegravir may well be cost effective in low income settings in sub-Saharan Africa.
- The level of pre-ART NNRTI drug resistance will be just one factor to consider when deciding on transition to dolutegravir.
- Studies (e.g. stepped-wedge trial) to understand the real-life impact of transitioning to dolutegravir first line regimens would seem appropriate to perform.

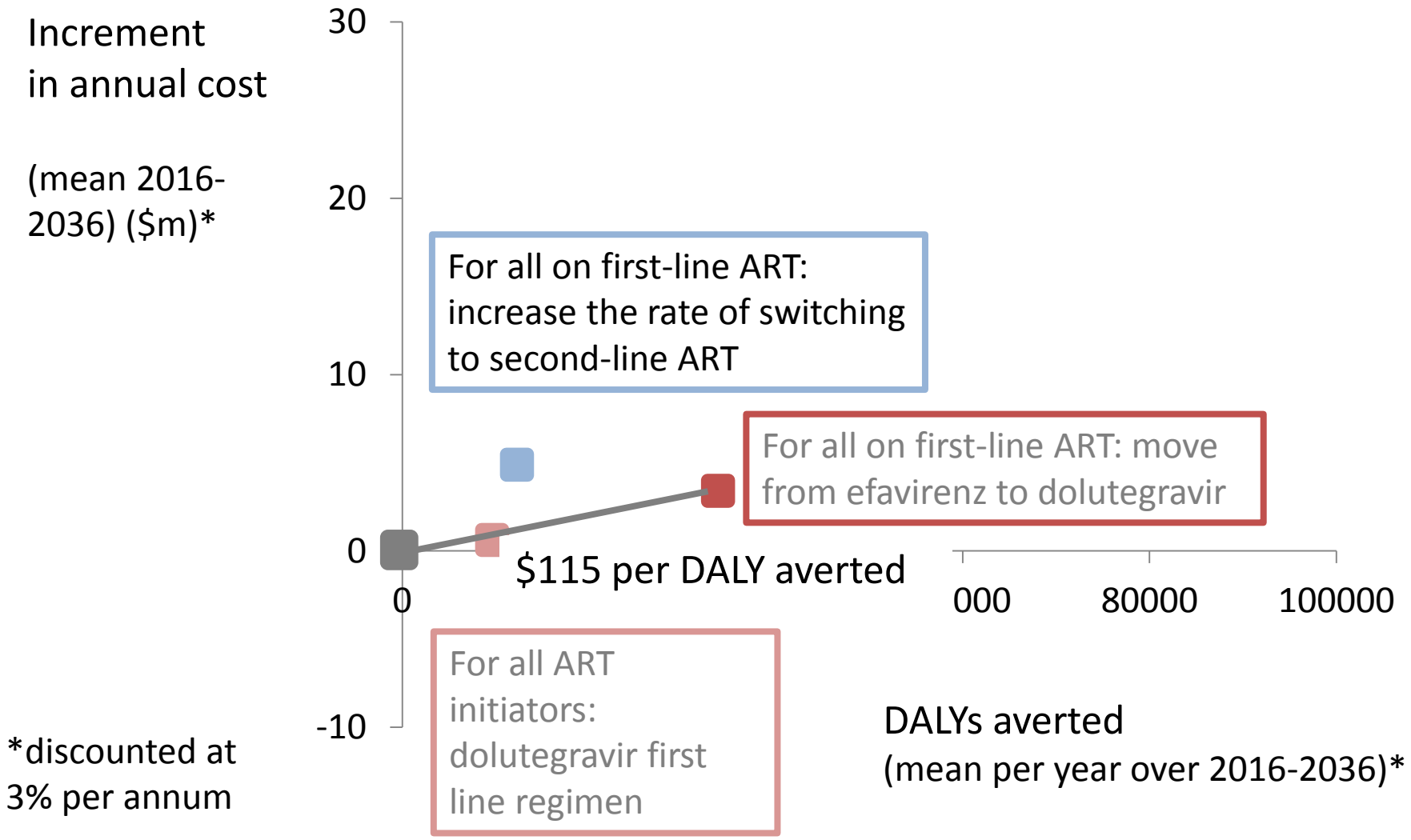
Acknowledgements

Working Group on Modelling Potential Responses to High Levels of pre-ART Drug Resistance in Sub-Saharan Africa

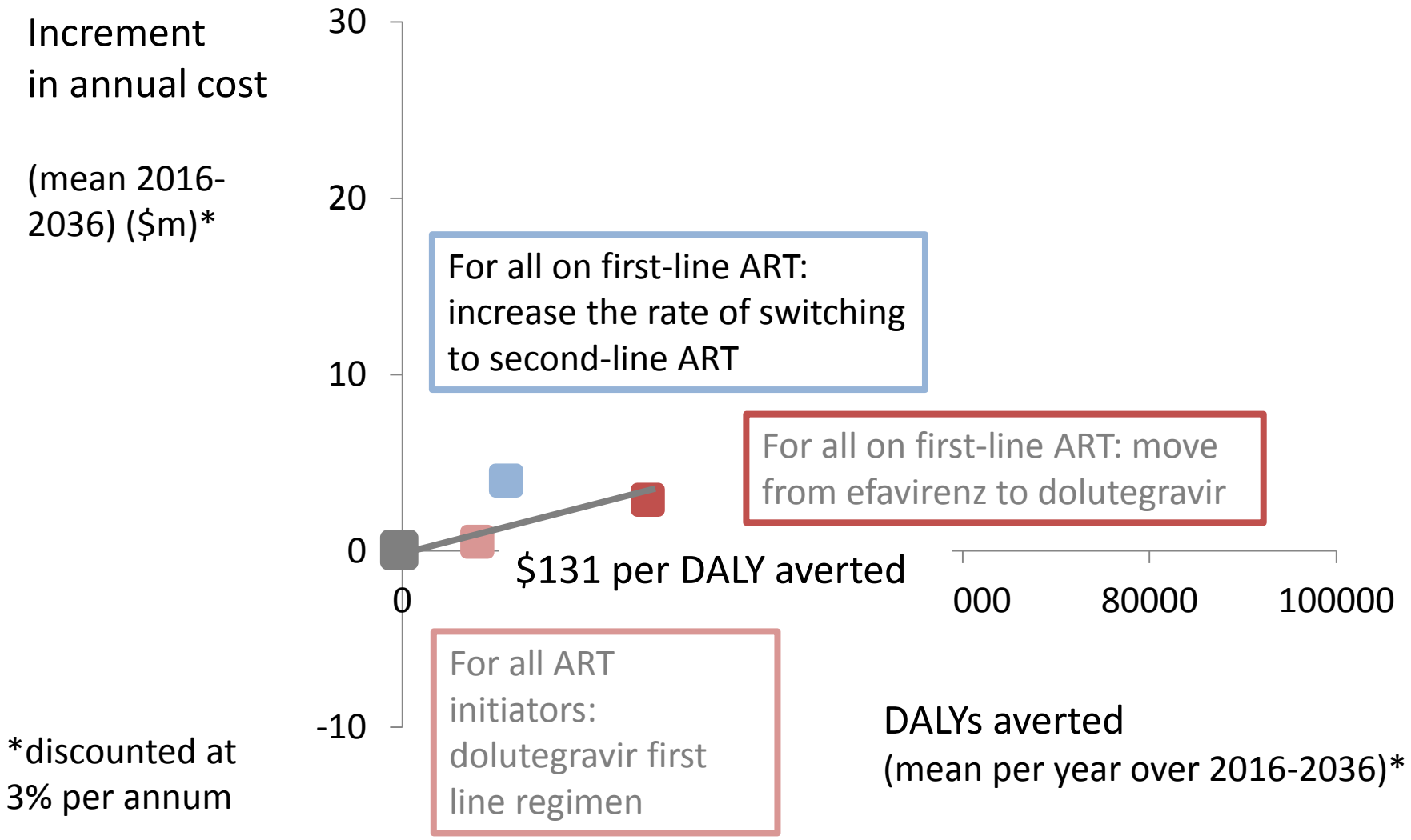
Silvia Bertagnolio Jhoney Barcarolo Valentina Cambiano Timothy Hallett Michael Jordan Meg Doherty Andrea De Luca Jens Lundgren Mutsa Mhangara John Mellors Fumiyo Nakagawa Brooke Nichols Urvi Parikh Elliot Raizes Paul Revill Deenan Pillay Tobias Rinke de Wit Kim Sigaloff David van de Vijver Marco Vitoria Raleigh Watts

Back-up slides

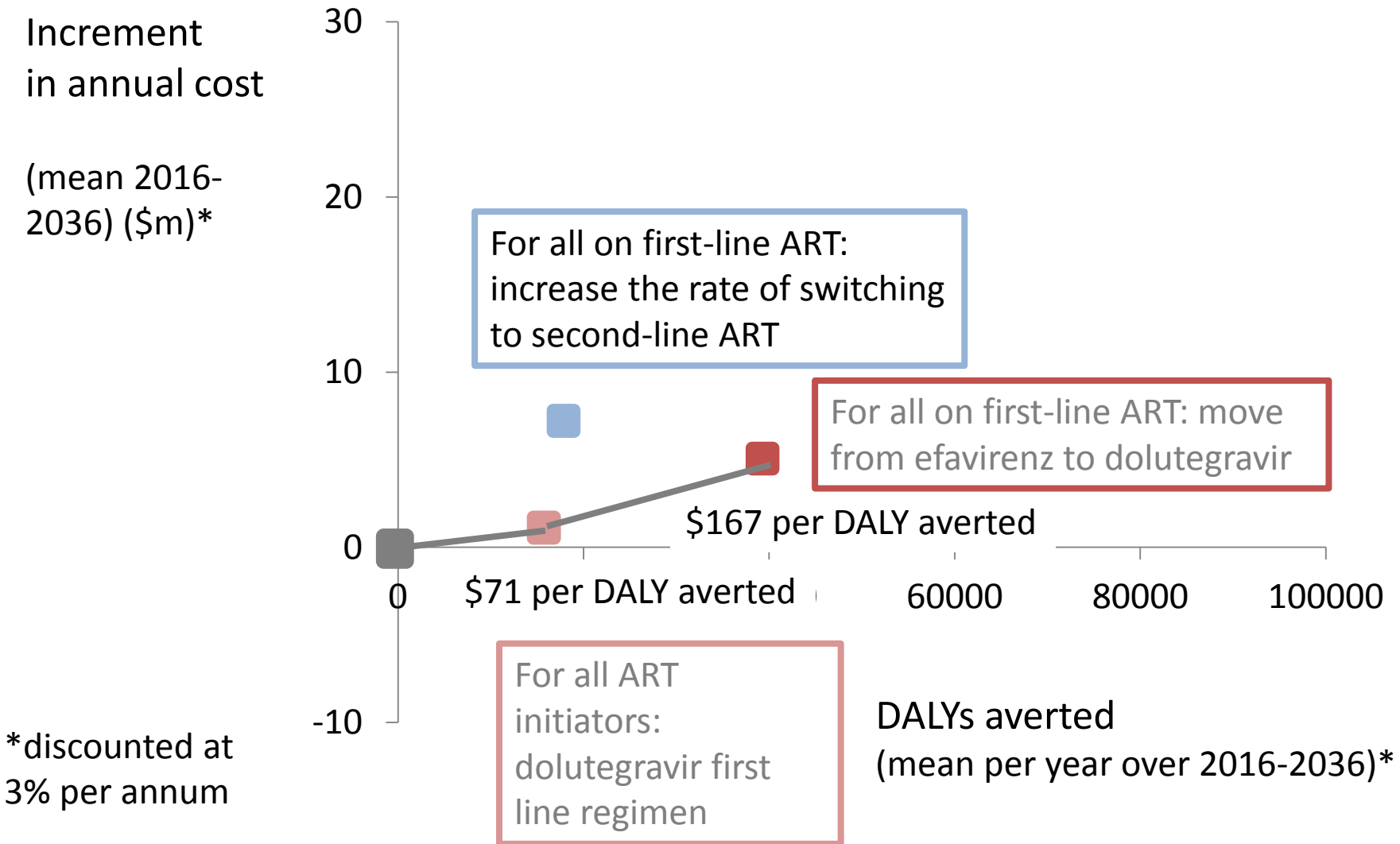
Increment in cost and DALYs averted relative to no change in policy if **5% - 10%** of all ART initiators have NNRTI resistance in 2016



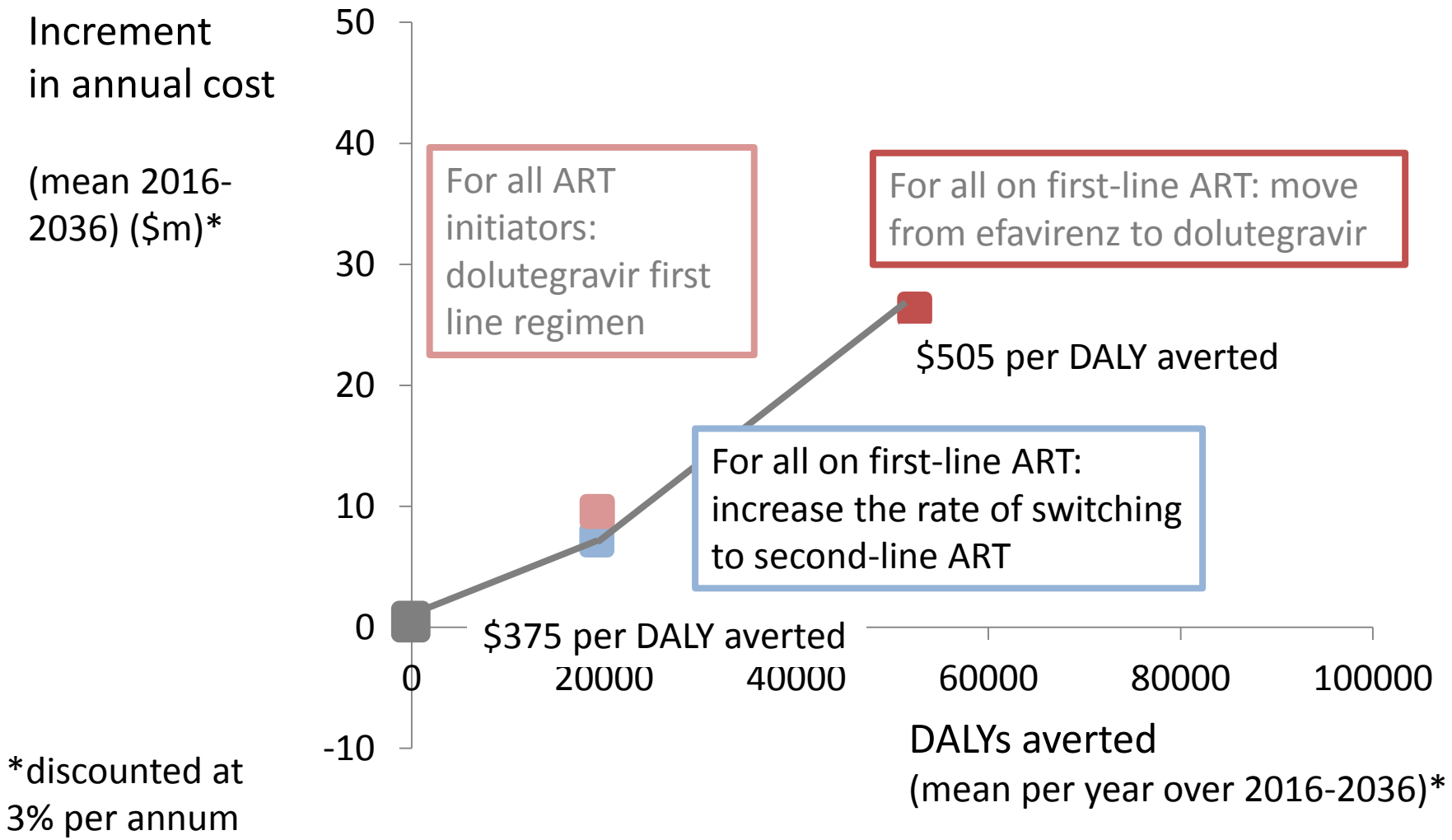
Increment in cost and DALYs averted relative to no change in policy if **< 5%** of all ART initiators have NNRTI resistance in 2016



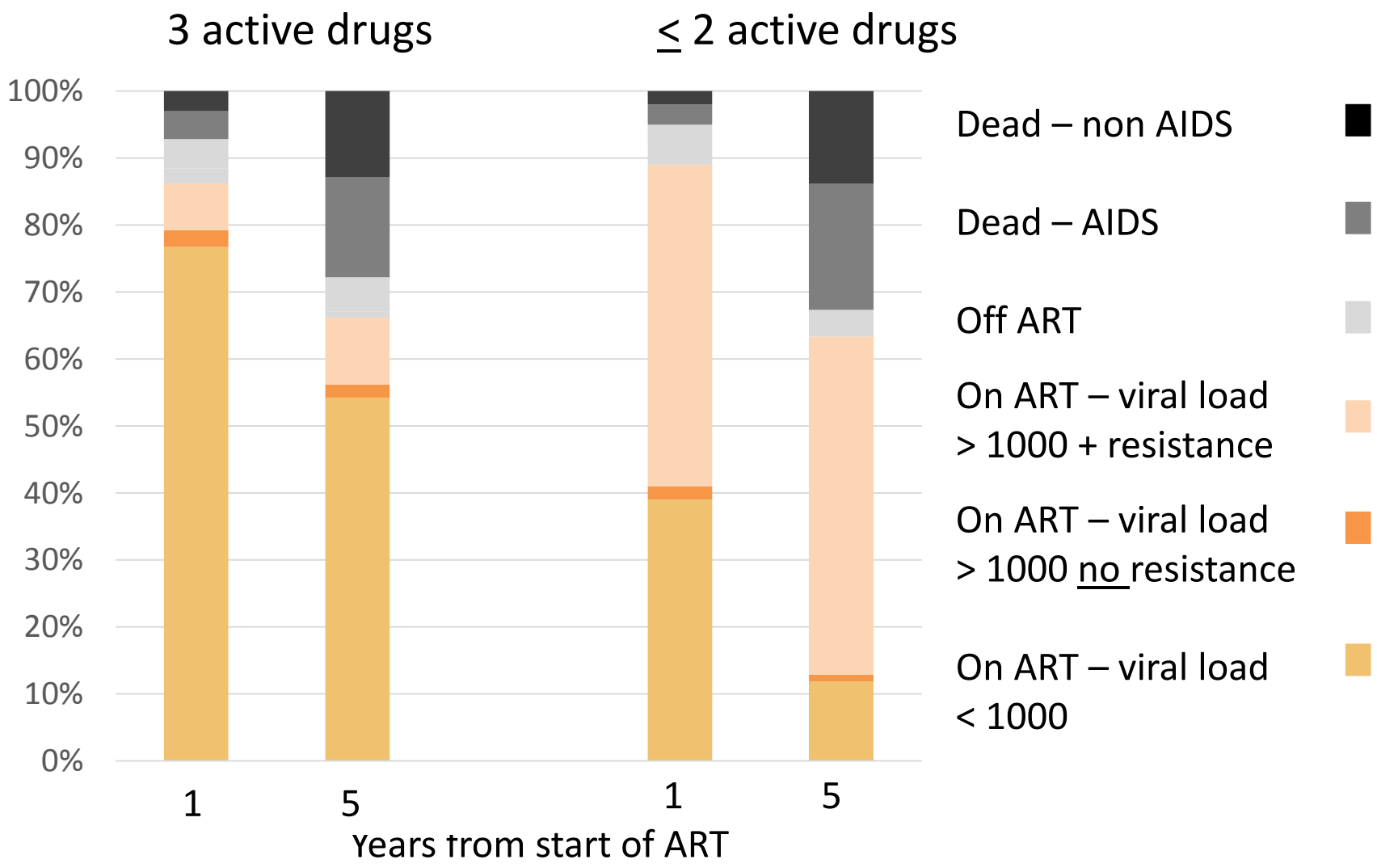
Sensitivity analysis: In context of higher rate of dolutegravir failure.



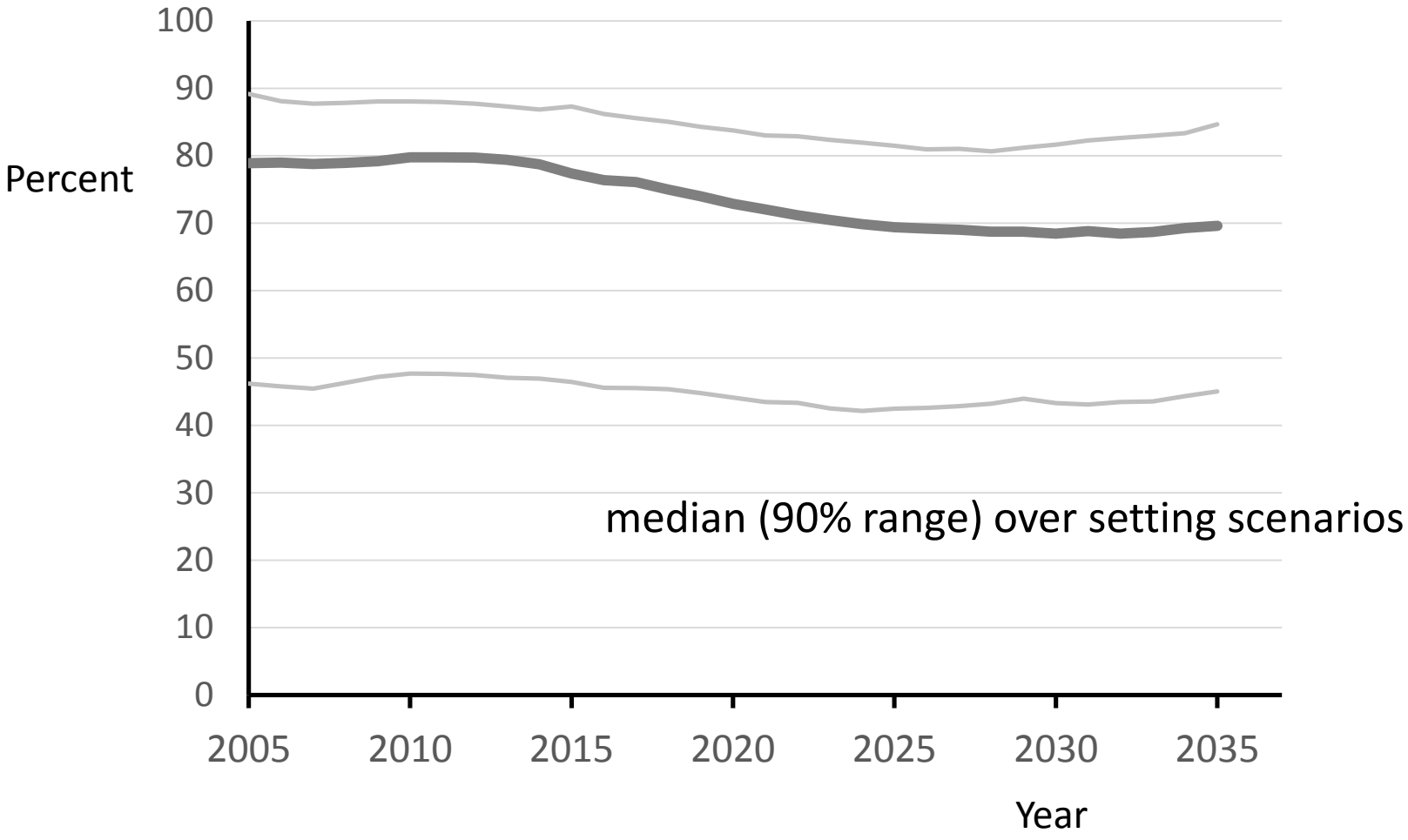
Sensitivity analysis: In context of 2-fold higher dolutegravir cost ($88 instead of $44)



Modelled outcomes of efavirenz-containing 1st-line regimens according to number of active drugs at ART start and no switching to second line



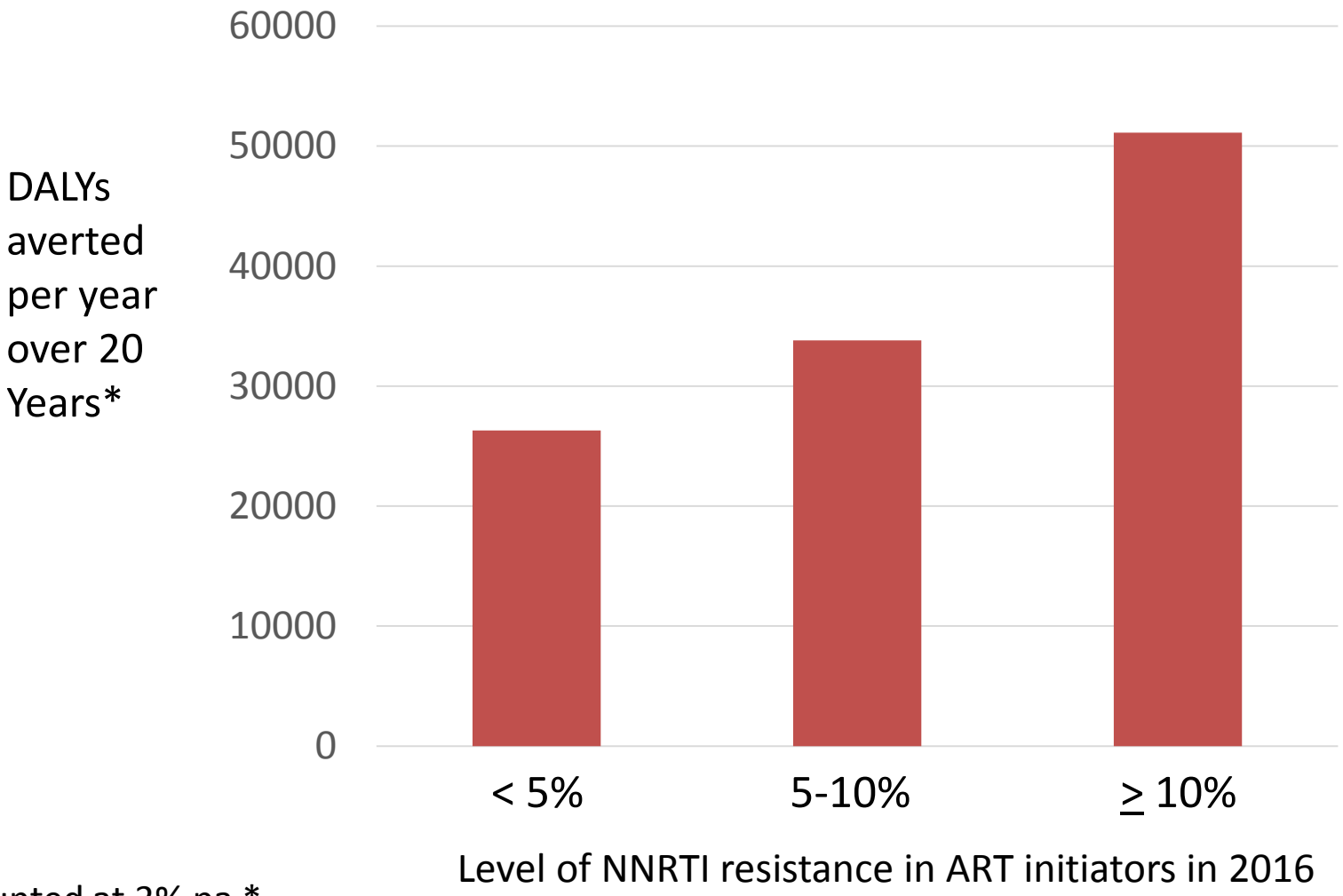
Plausible range over settings in proportion of people with viral load < 1000 cps/mL at 1 year from start of ART* if there are no programmatic changes



*amongst those alive (but not necessarily under care) 1 year after start of ART

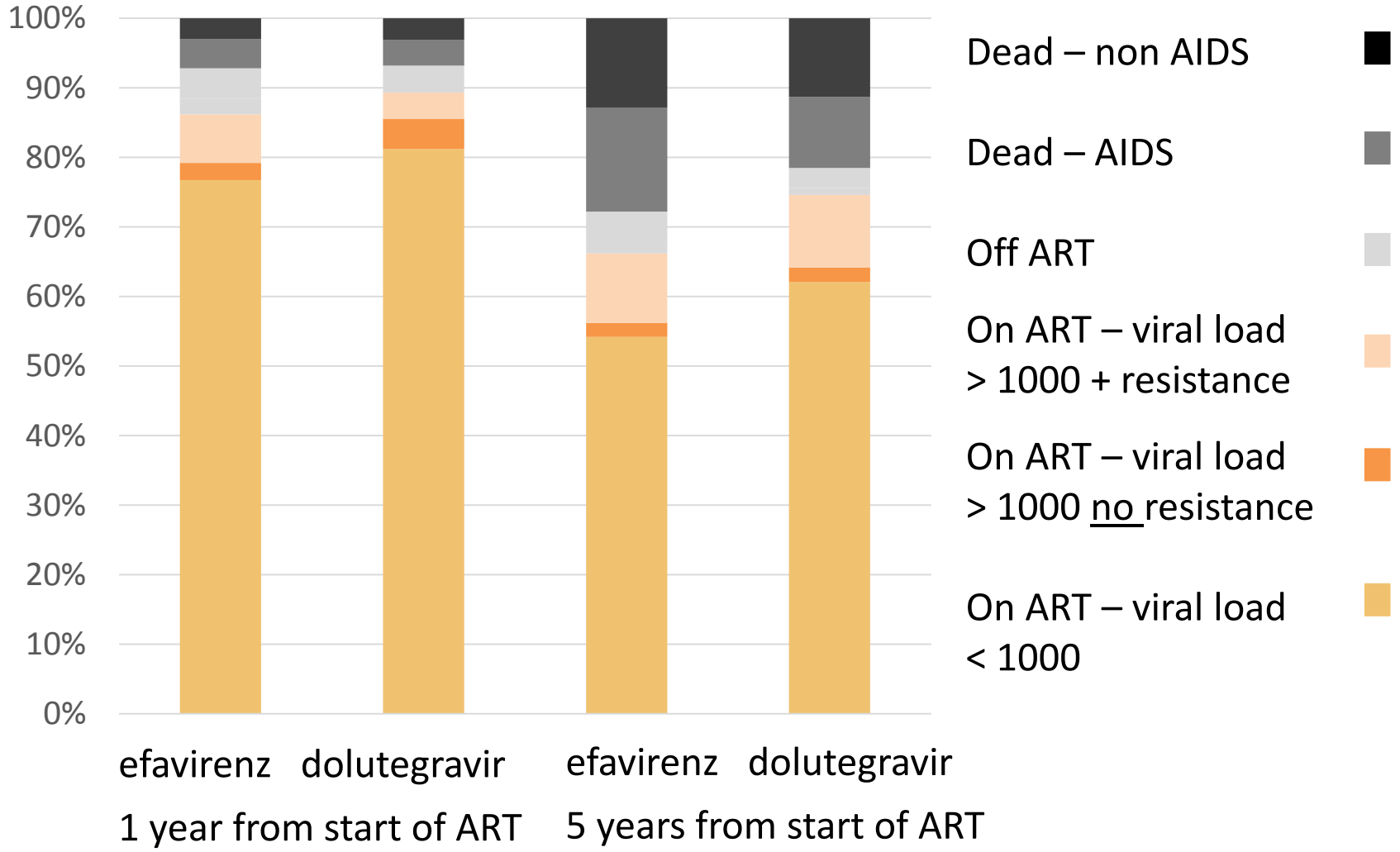
3 year moving average

DALY benefit from move from efavirenz to dolutegravir according to level of NNRTI resistance in ART initiators in 2016



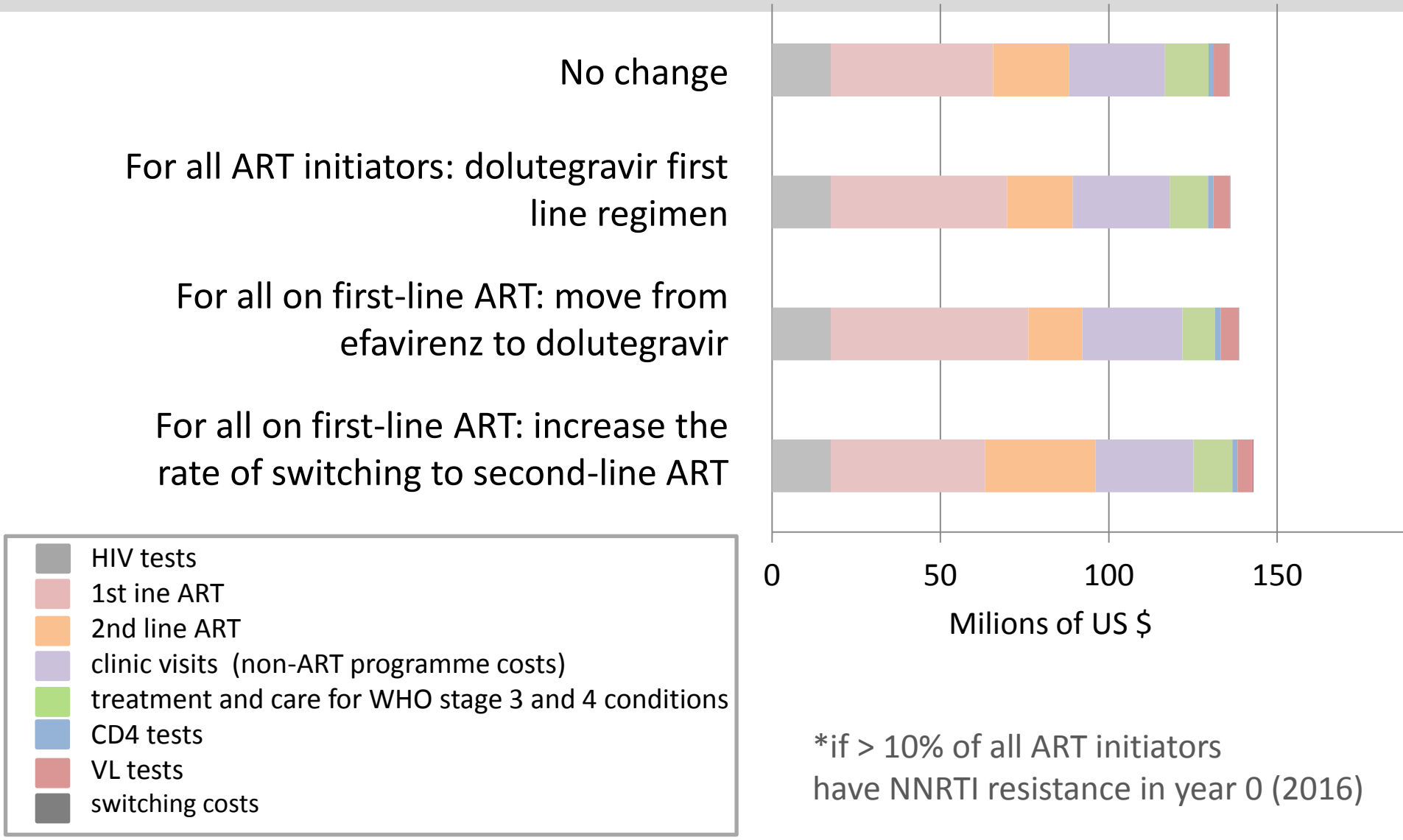
Discounted at 3% pa *

Modelled outcomes of efavirenz- and dolutegravir- containing 1st-line regimens in context of ≥ 3 active drugs at ART start and no switching to second line



Total cost according to policy*

(mean annual cost over 2016-2036, discounted at 3% per annum)



*if > 10% of all ART initiators have NNRTI resistance in year 0 (2016)