CLINICAL IMPACT: NOVEL WHO (& IAS-USA) HIV-RESISTANCE GUIDELINES

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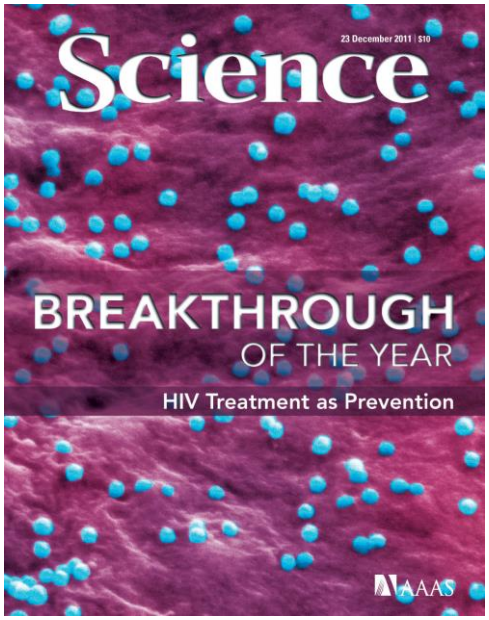
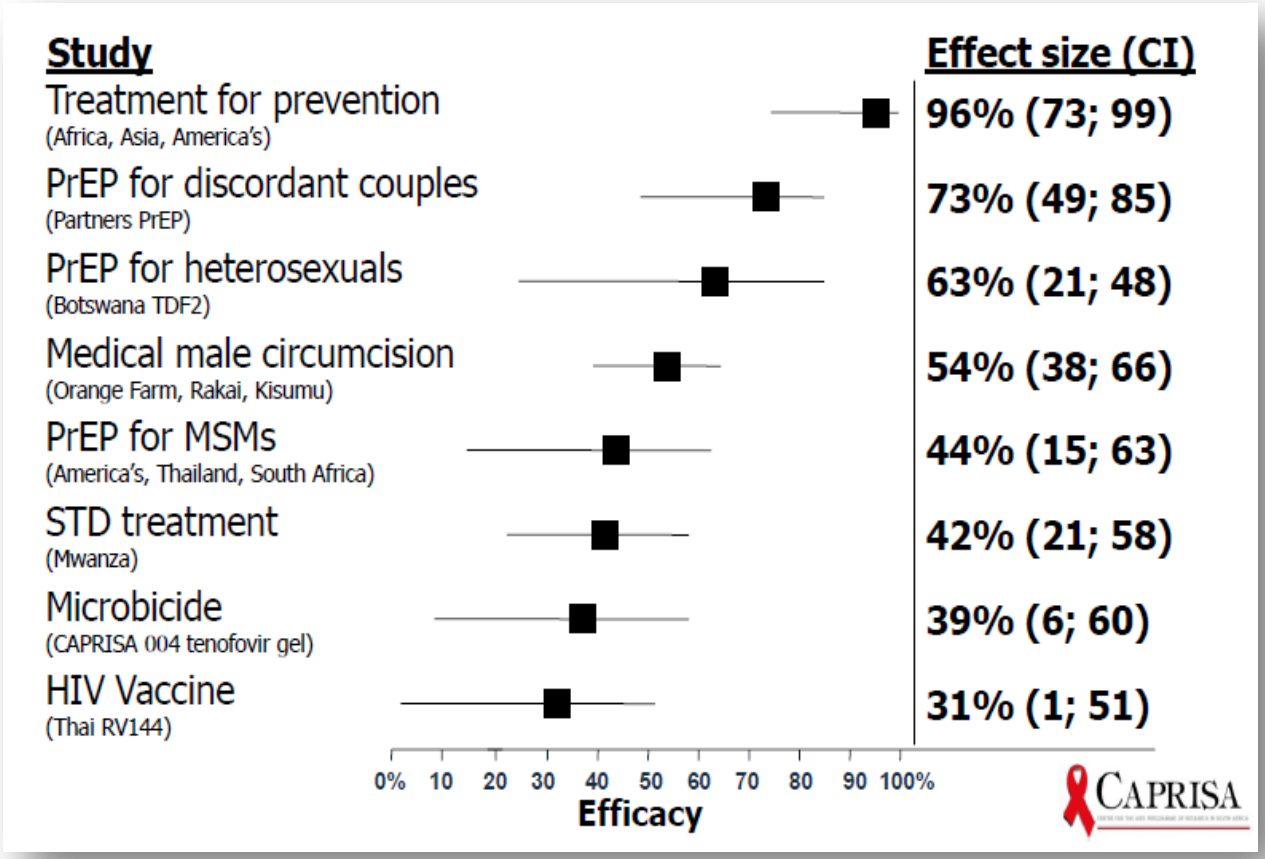
Who should be treated?

WHO recommends initiation of ART for all people living with HIV at any CD4 cell count

HIV treatment **is** prevention



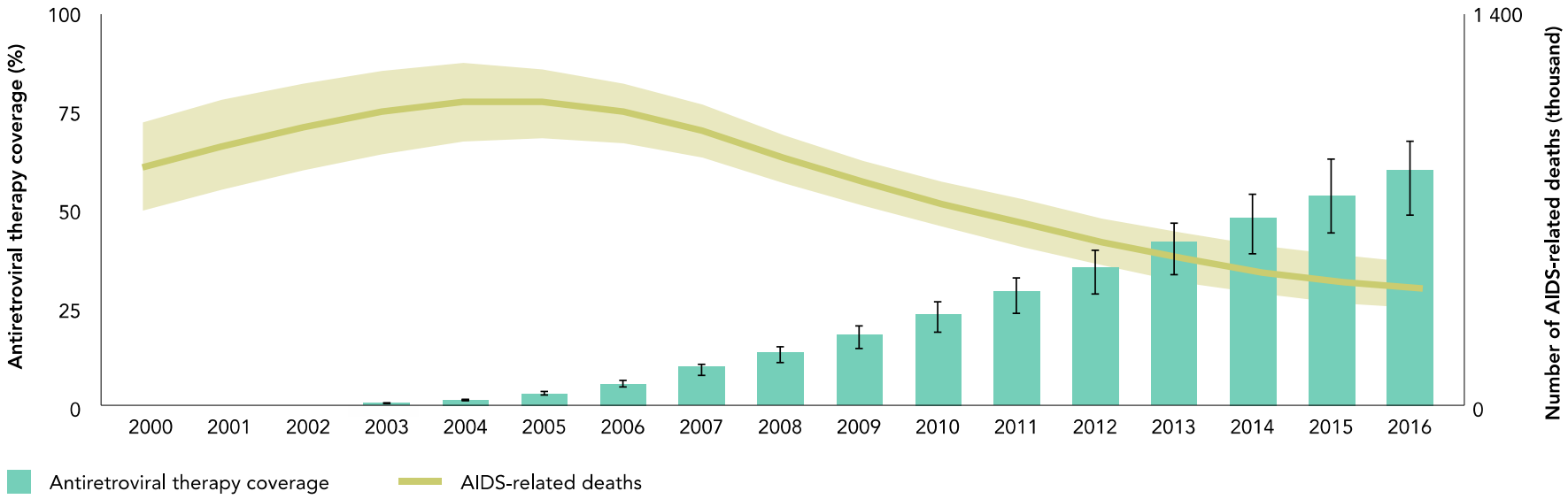


Public health approach to ART

To support simplification of HIV treatment, WHO recommends a limited formulary of preferred treatment options. As well as giving priority to antiretroviral drugs (ARVs) with superior efficacy and tolerability, WHO prioritizes choices based on:

- convenience,
- availability as fixed dose combinations (FDCs),
- compatibility with treatment of common co-morbidities, and
- potential to use across all populations.

AIDS-RELATED DEATHS NEARLY CUT IN HALF IN SIX YEARS

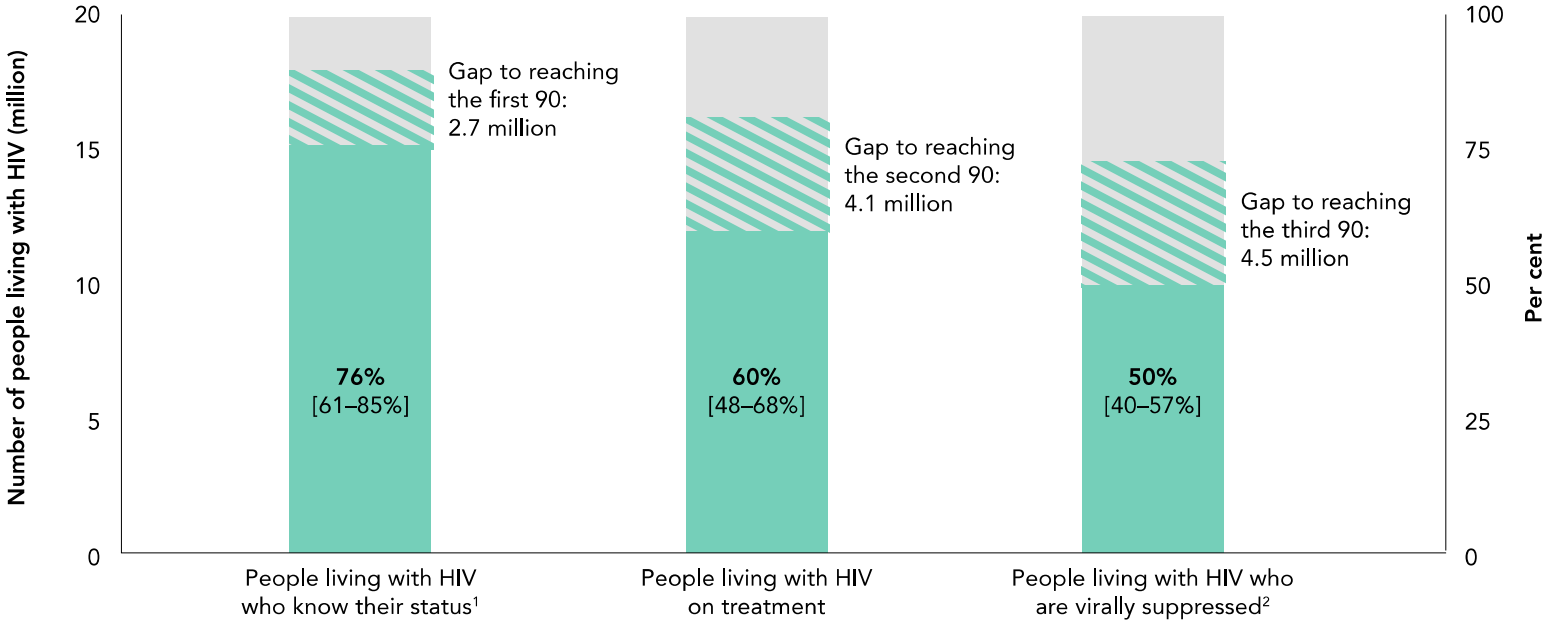


ANTIRETROVIRAL THERAPY COVERAGE AND NUMBER OF AIDS-RELATED DEATHS, EASTERN AND SOUTHERN AFRICA, 2000–2016

Antiretroviral therapy scale-up has been largely responsible for a steep decline in AIDS-related mortality in eastern and southern Africa: the estimated 420 000 [350 000–510 000] AIDS-related deaths in 2016 were 42% fewer than in 2010. The drop in deaths due to AIDS-related illnesses has been even greater among children (aged 0–14 years), declining from an estimated 130 000 [99 000–150 000] in 2010 to 58 000 [41 000–80 000] in 2016. AIDS-related illnes remains a leading cause of death in the region, however, especially among young women and girls aged 15–24 years *(1)*.

Source: 2017 Global AIDS Monitoring; UNAIDS 2017 estimates.

HIV TESTING AND TREATMENT CASCADE IN EASTERN AND SOUTHERN AFRICA



KNOWLEDGE OF HIV STATUS, ANTIRETROVIRAL THERAPY COVERAGE AND VIRAL SUPPRESSION AMONG PEOPLE LIVING WITH HIV, EASTERN AND SOUTHERN AFRICA, 2016

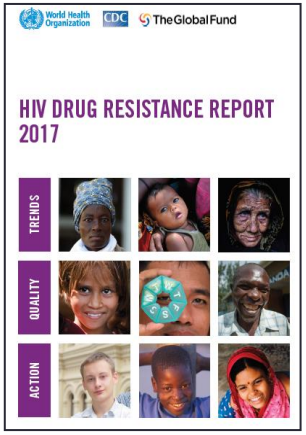
Source: UNAIDS special analysis, 2017; see annex on methods for more details.

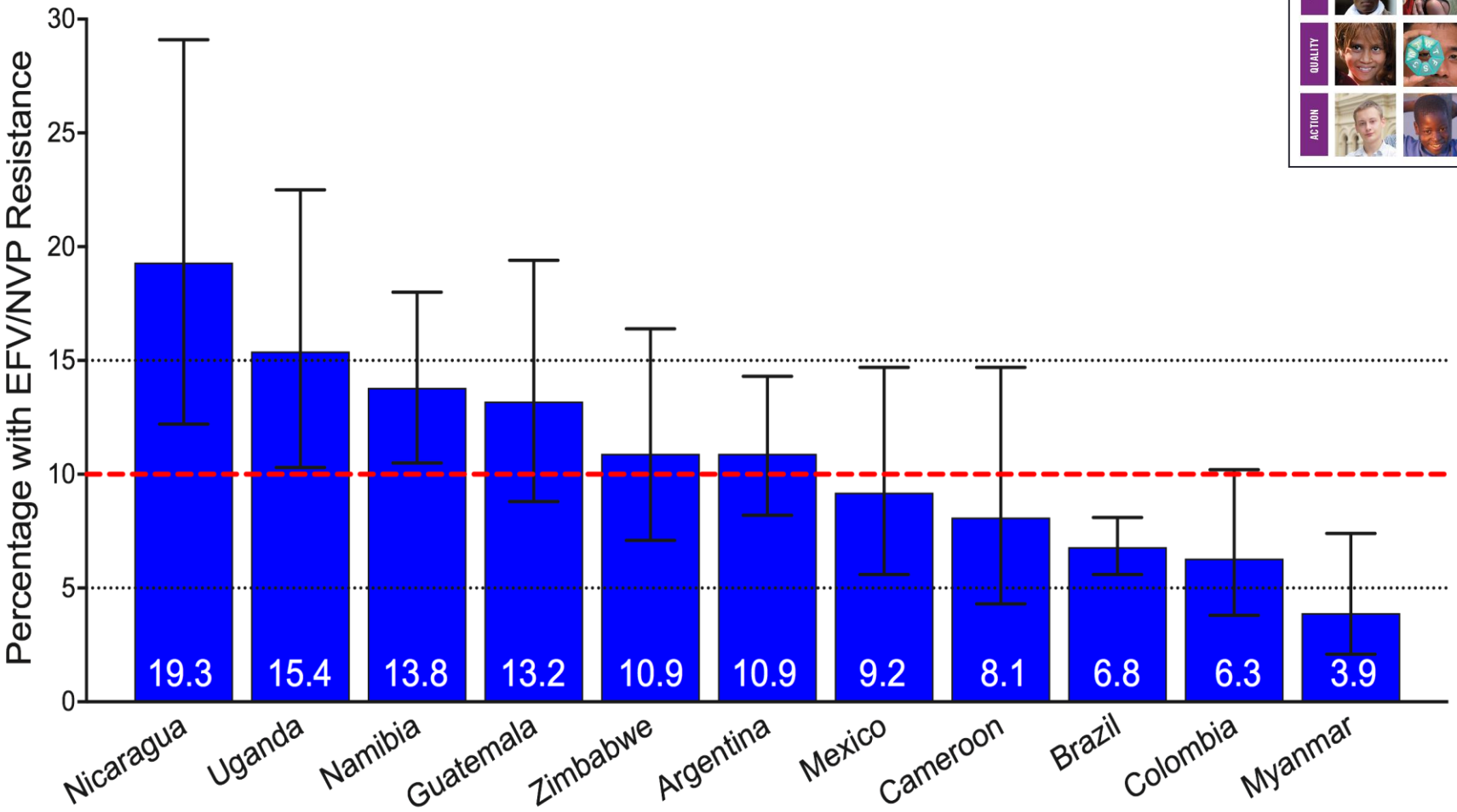
[1] 2016 measure derived from data reported by 17 countries, which accounted for 99% of people living with HIV in western and central Africa.

[2] 2016 measure derived from data reported by 11 countries. Regionally, 37% of all people on antiretroviral therapy were reported to have received a viral load test during the reporting period.

PRETREATMENT HIVDR IN PEOPLE INITIATING ART

WHO's Report on HIV drug resistance 2017





NNRTI resistance pandemic

HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis

Ravindra K Gupta, John Gregson, Neil Parkin, Hiwot Haile-Selassie, Amilcar Tanuri, Liliana Andrade Forero, Pontiano Kaleebu, Christine Watera, Avelin Aghokeng, Nicholus Mutenda, Janet Dzangare, San Hone, Zaw Zaw Hang, Judith Garcia, Zully Garcia, Paola Marchorro, Enrique Beteta, Amalia Giron, Raph Hamers, Seth Inzaule, Lisa M Frenkel, Michael H Chung, Tulio de Oliveira, Deenan Pillay, Kogie Naidoo, Ayesha Kharsany, Ruthiran Kugathasan, Teresa Cutino, Gillian Hunt, Santiago Avila Rios, Meg Doherty, Michael R Jordan, Silvia Bertagnolio

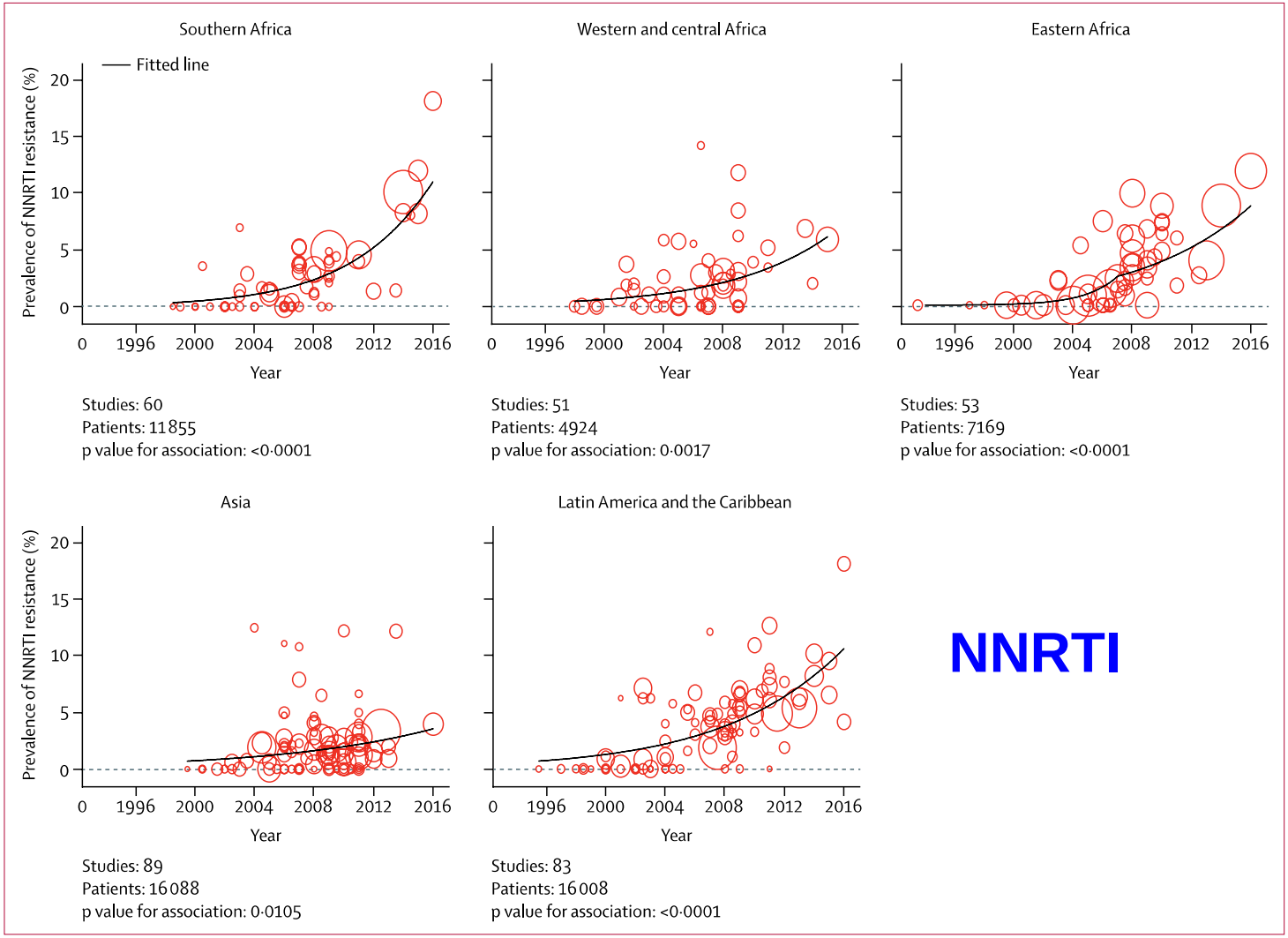
	Number of studies	Number of genotypes	Genotypes per study	Sampling year	Studies in urban populations*
Eastern Africa	53	7169	92 (57–187)	2008 (2005–09)	32/44 (73%)
Southern Africa	61	11 855	102 (53–108)	2007 (2004–09)	41/47 (87%)
Western and central Africa	56	4924	79 (49–104)	2007 (2004–09)	48/50 (96%)
Latin America and the Caribbean	90	16 008	98 (52–221)	2008 (2003–10)	67/69 (97%)
Asia†	98	16 088	97 (47–223)	2009 (2006–10)	89/89 (100%)
Overall	358	56 044	95 (50–194)	2008 (2005–10)	277/299† (93%)

Data are n, median (IQR), or n/N (%). *Denominators restricted to studies with unambiguous information on location available. †For the purpose of this analysis, countries in the southeast Asia, the western Pacific, and eastern Mediterranean regions and Turkey (Europe region) are grouped under the regional heading of Asia.

Table 1: **Characteristics of included studies by region**

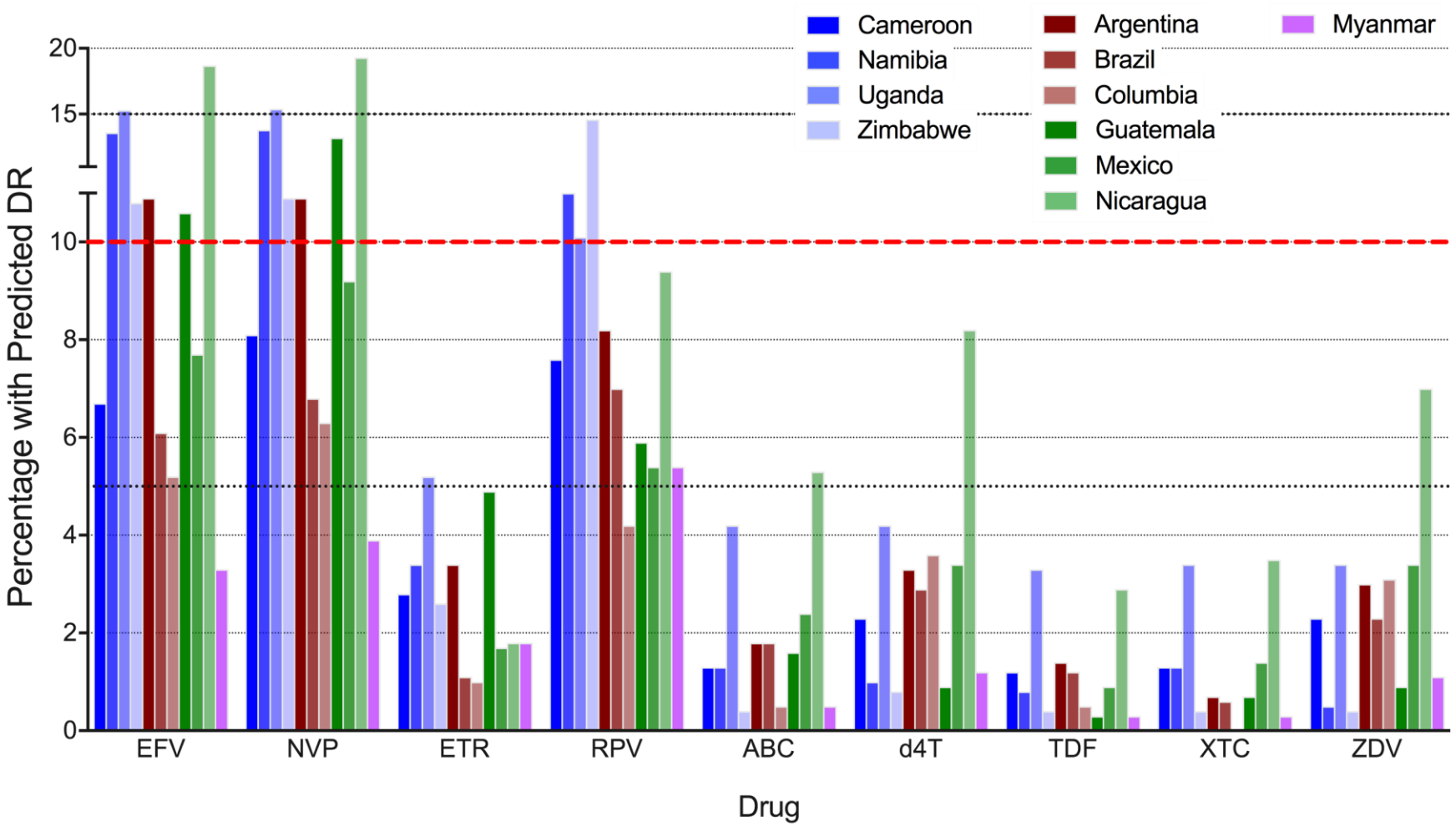
Gupta et al, Lancet Infect Dis 2018

NNRTI resistance pandemic



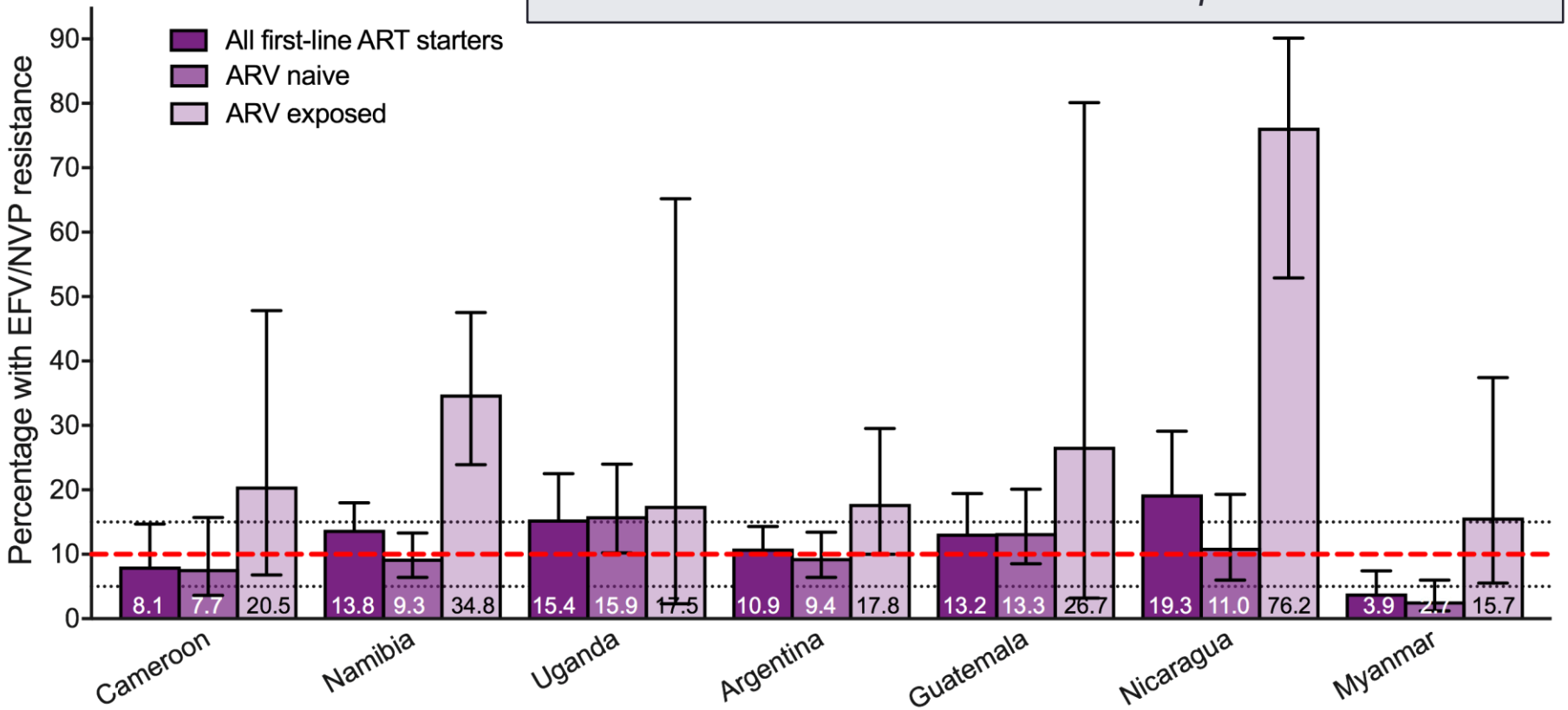
Gupta et al, Lancet Infect Dis 2018

Pretreatment HIVDR in first-line ART initiators by drug (national surveys), 2014-2016



PDR to EFV/NVP in first-line starters: naive vs with previous exposure to ARVs (national surveys), 2014-16

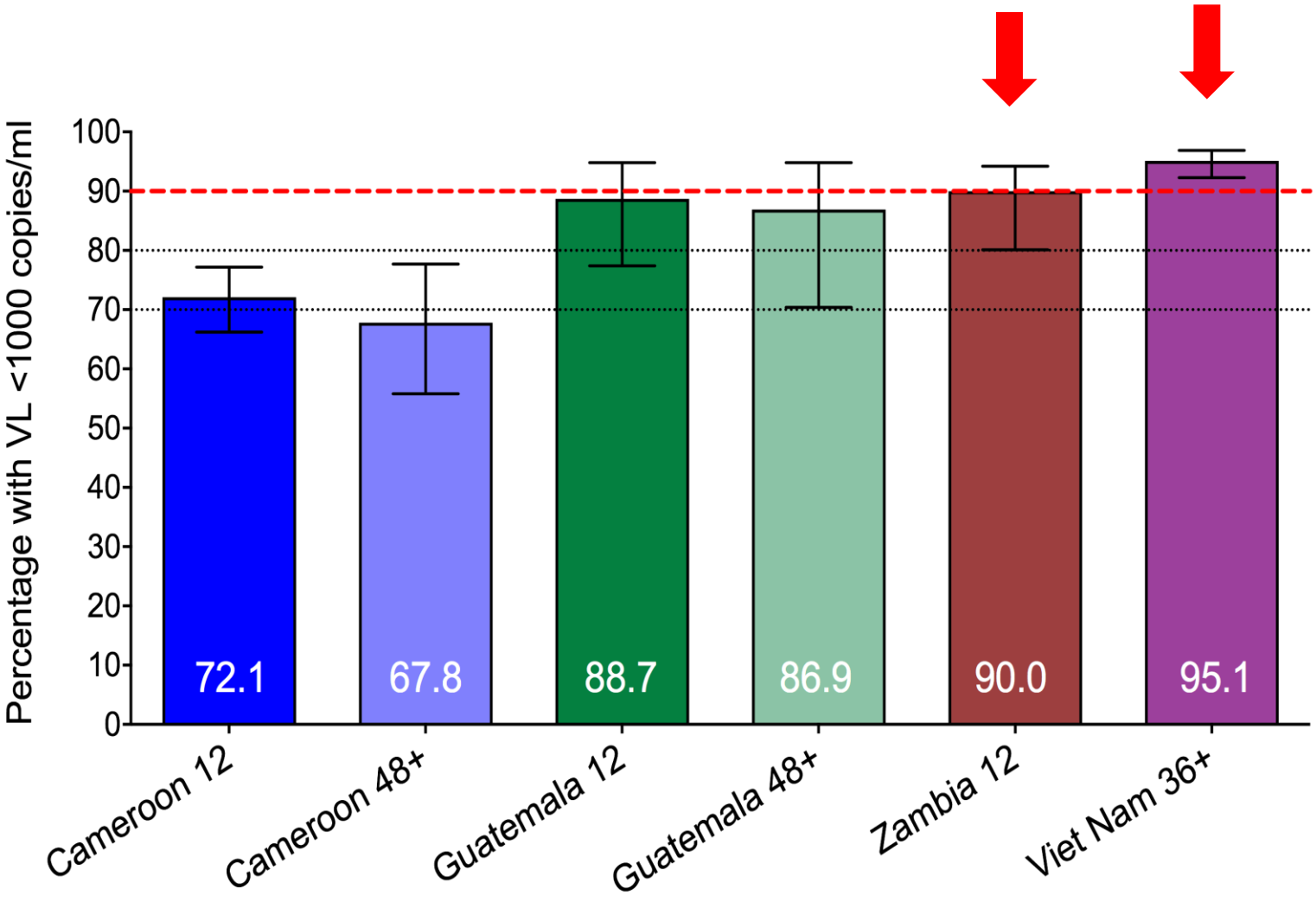
Prior exposed to ARV….21.6% (95% CI 13.8-32.2)
ARV drug naïve ……..8.3% (95% CI 6-11.4)
p <0.0001



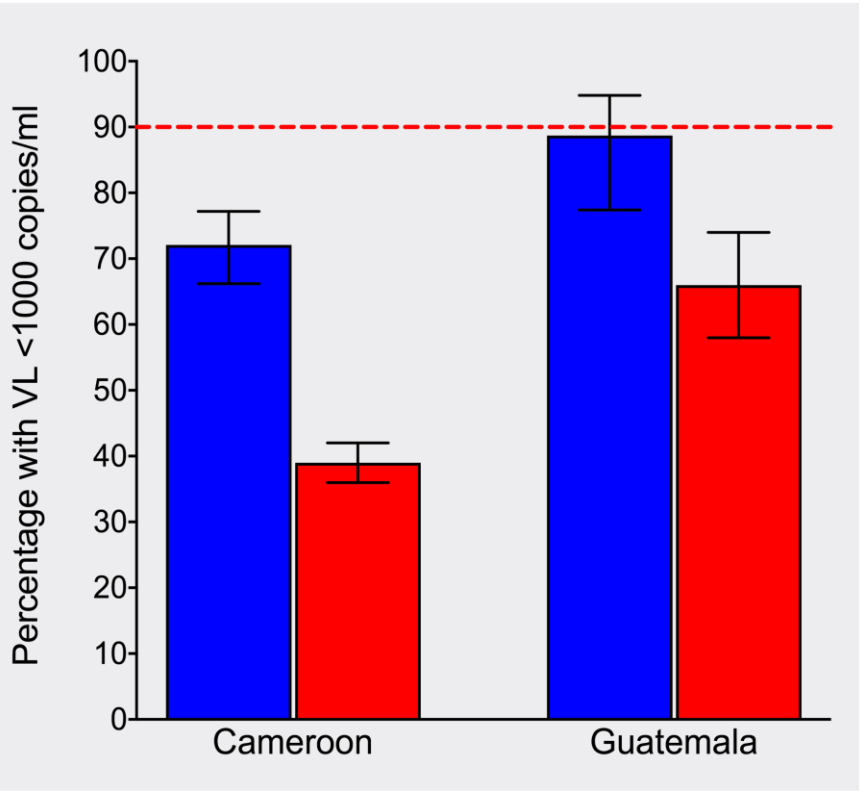
	Cameroon	Namibia	Uganda	Argentina	Guatemala	Nicaragua	Myanmar
% w prior ARV exposure	7.8%	18.0%	1.2%	18.6%	2.8%	12.3%	8.4%

ACQUIRED HIVDR IN PEOPLE RECEIVING ART

Viral load suppression in people retained on ART (national surveys), 2014-2016

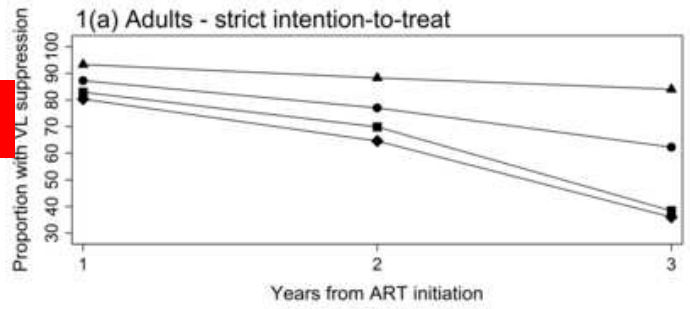


VL suppression in people retained in care *vs* "ITT" analysis (not in care=VF)



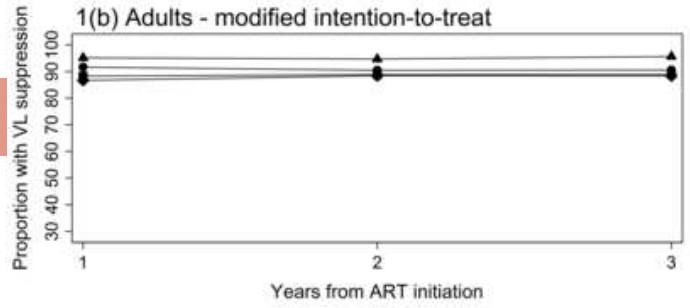
National surveys, 2014-2016

45%



Total patients			
Asia-Pacific	1842	1358	920
CCASAnet	2918	2097	1240
North America	11677	6884	3223
South Africa	11441	7041	3872

90%



Total patients			
Asia-Pacific	1806	1266	808
CCASAnet	2777	1784	852
North America	10970	5410	1392
South Africa	10600	5142	1577

IeDEA cohort: *Jiamsakul A, et al . JAIDS, 2017*

Asia-Pacific CCASAnet North America South Africa

People with NNRTI PDR initiating EFV/NVP had worse outcomes compared to people initiating an non-NNRTI regimen (7 studies)

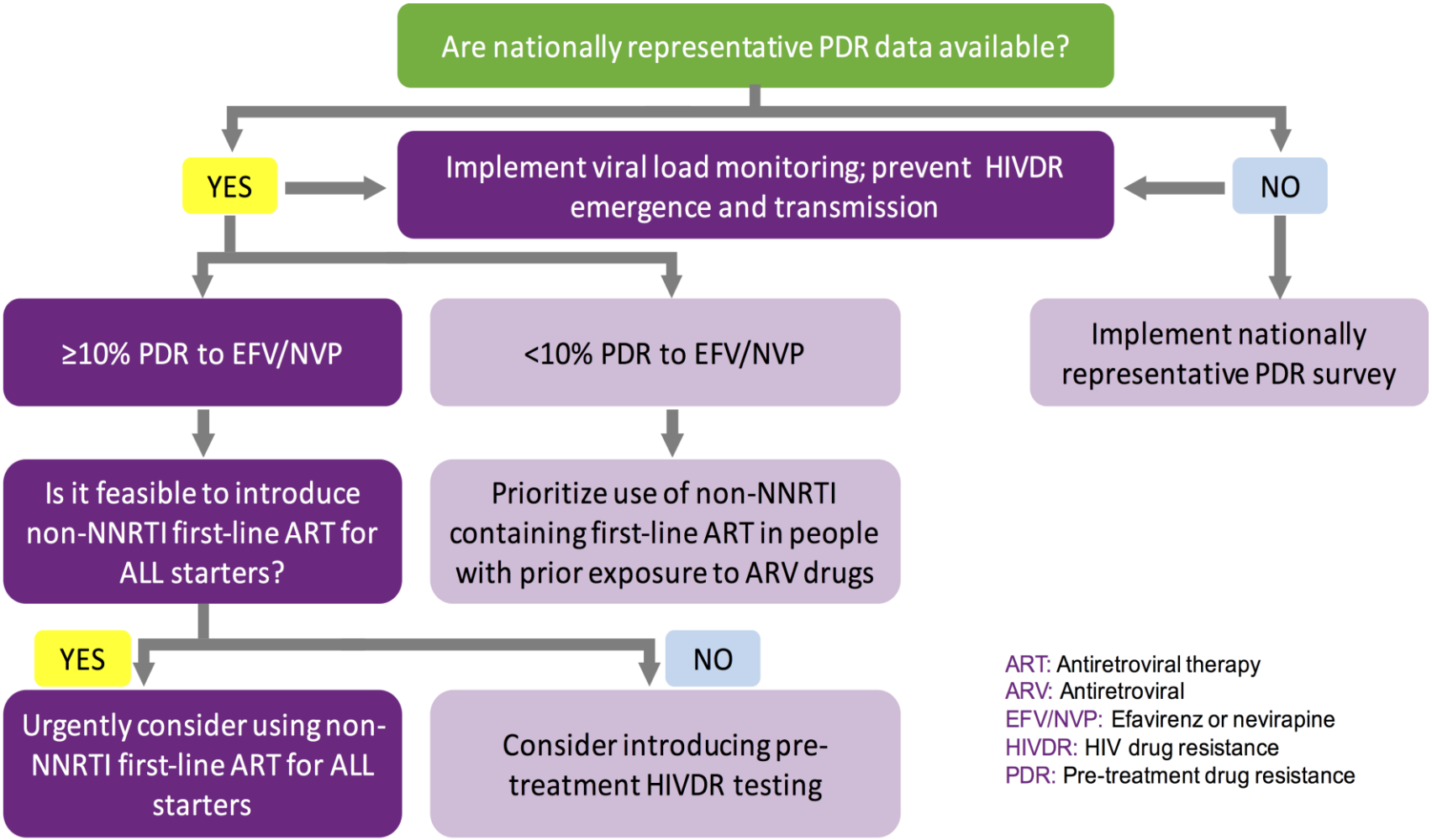
Outcomes	Odds Ratio	95% CI
Less likely to achieve virological suppression	0.66	0.45-0.97
Shorter time to virological failure or death	HR 3.6	1.7-7.5
More likely to discontinue ART	8.70	3.51-21.53

The cost of no action

Impact of pretreatment HIVDR in sub-Saharan Africa			
In the context of level of pretreatment HIVDR ≥ 10%			
	AIDS deaths	New infections	ART costs
Fast-track projections (with HIVDR)	5.6 million	5.1 million	$83 billion
Percentage attributable to HIVDR (2016-2030)	15.97%	8.74%	7.71%
Amount attributable to HIVDR (2016-2030)	890 000	450 000	$6.5 billion

J.Stover et al. PLoS ONE 2016 *Phillips AN,. J Infect Dis. 2017*

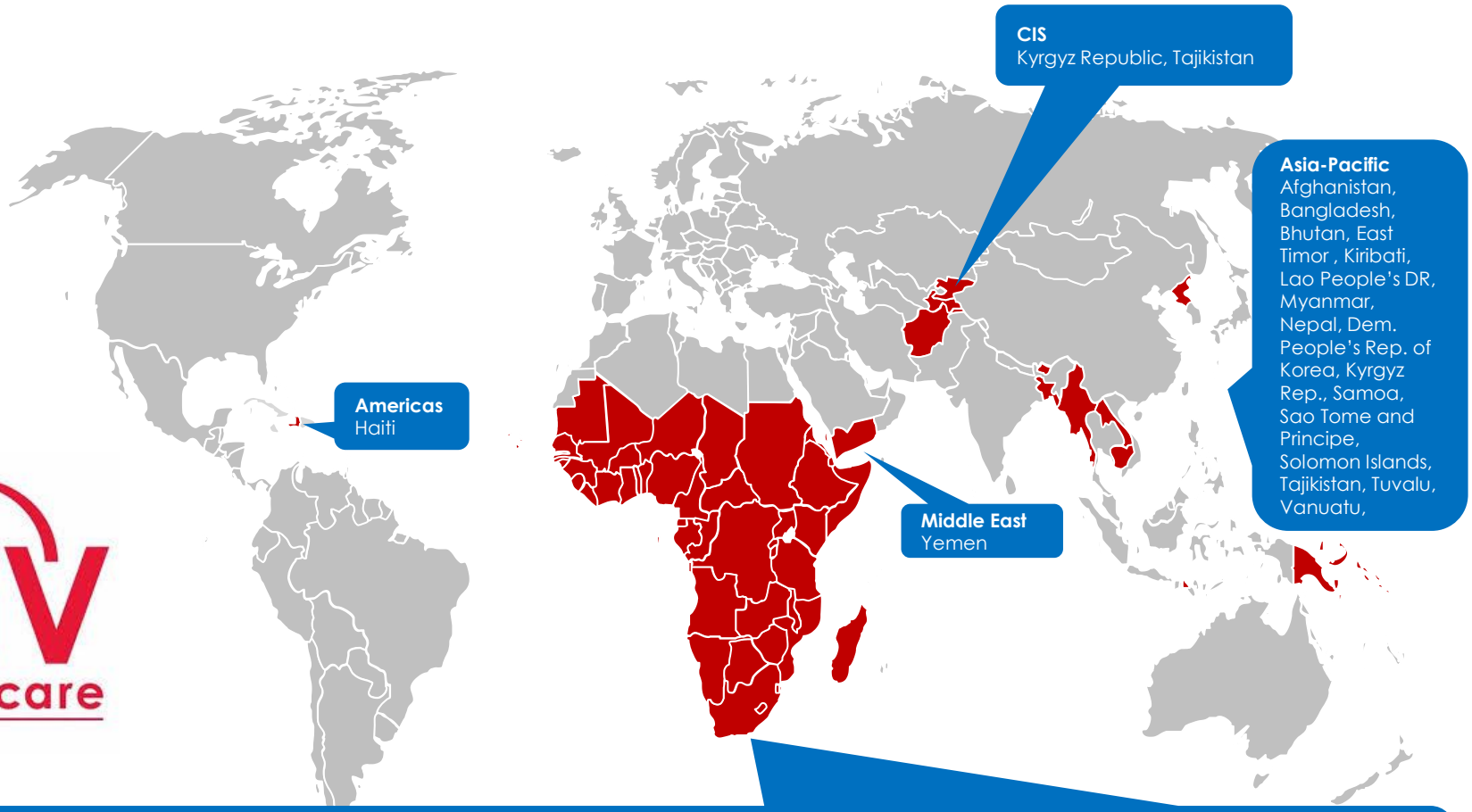
WHO recommended response to pretreatment HIV drug resistance



ART: Antiretroviral therapy
ARV: Antiretroviral
EFV/NVP: Efavirenz or nevirapine
HIVDR: HIV drug resistance
PDR: Pre-treatment drug resistance

Royalty Free Voluntary Licence Adult Countries

16 generic manufacturers licensed to produce the current ViiV portfolio royalty free for 67 countries in Africa, Asia-Pacific and the Caribbean



ViiV Healthcare

Sub-Saharan Africa
Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Cote d'Ivoire, Djibouti, DR Congo (Zaire), Equatorial Guinea, Eritrea, Ethiopia, Gabon, Ghana, Gambia, Guinea, Guinea Bissau, Haiti, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, South Sudan, Sudan, Swaziland, Tanzania, Togo, Uganda, Zambia, Zimbabwe

Health benefits in responding to NNRTI PDR >10%* in sub-Saharan Africa according to the intervention

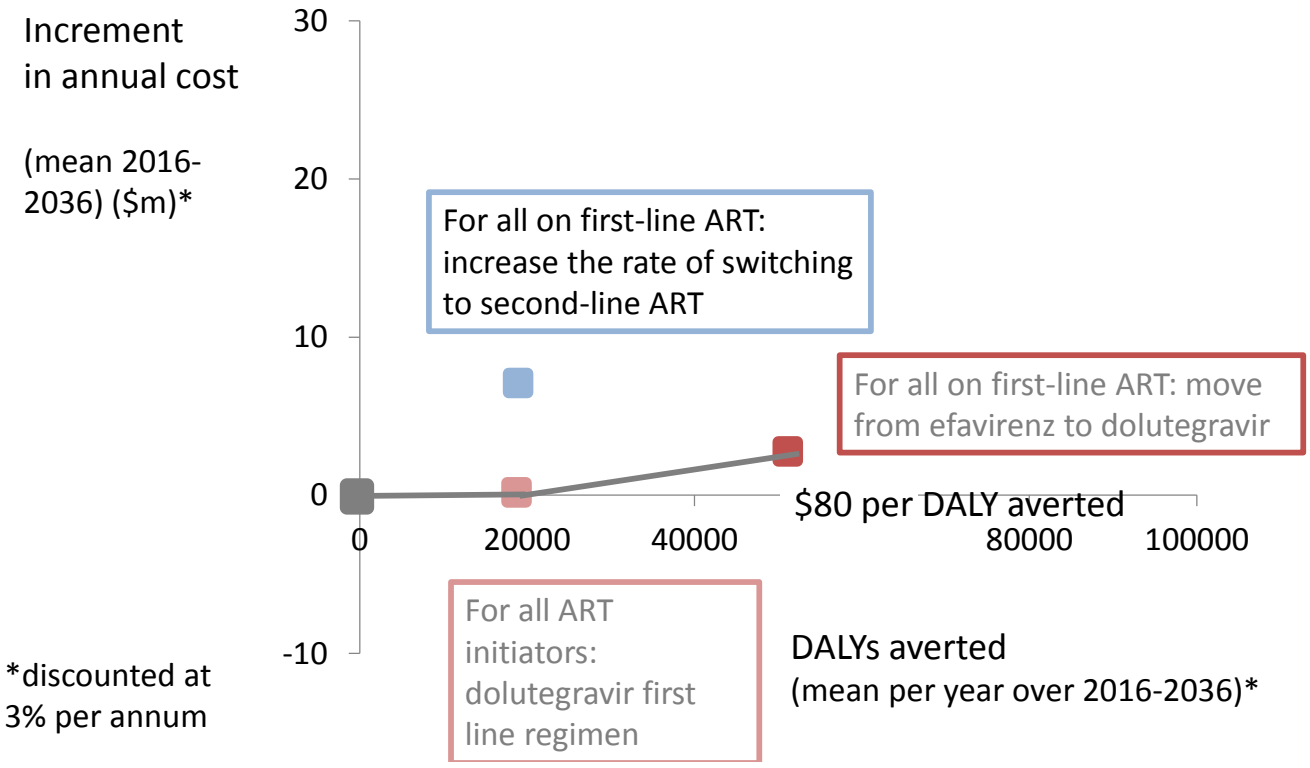
INTERVENTIONS	Viral load suppression (< 1000 c/mL) Mean %	Mortality Mean rate in people on ART /100 person year	HIV incidence Mean rate/100 person years
1. DTG in first-line ART	86%	3.5	0.72
2. Pretreatment HIVDR testing	83%	3.9	0.74
BASE CASE: EFV in first-line ART	77%	4.5	0.79

A.Phillips et al, in press, Lancet HIV

*(median 19%; IQR 14% - 26%)

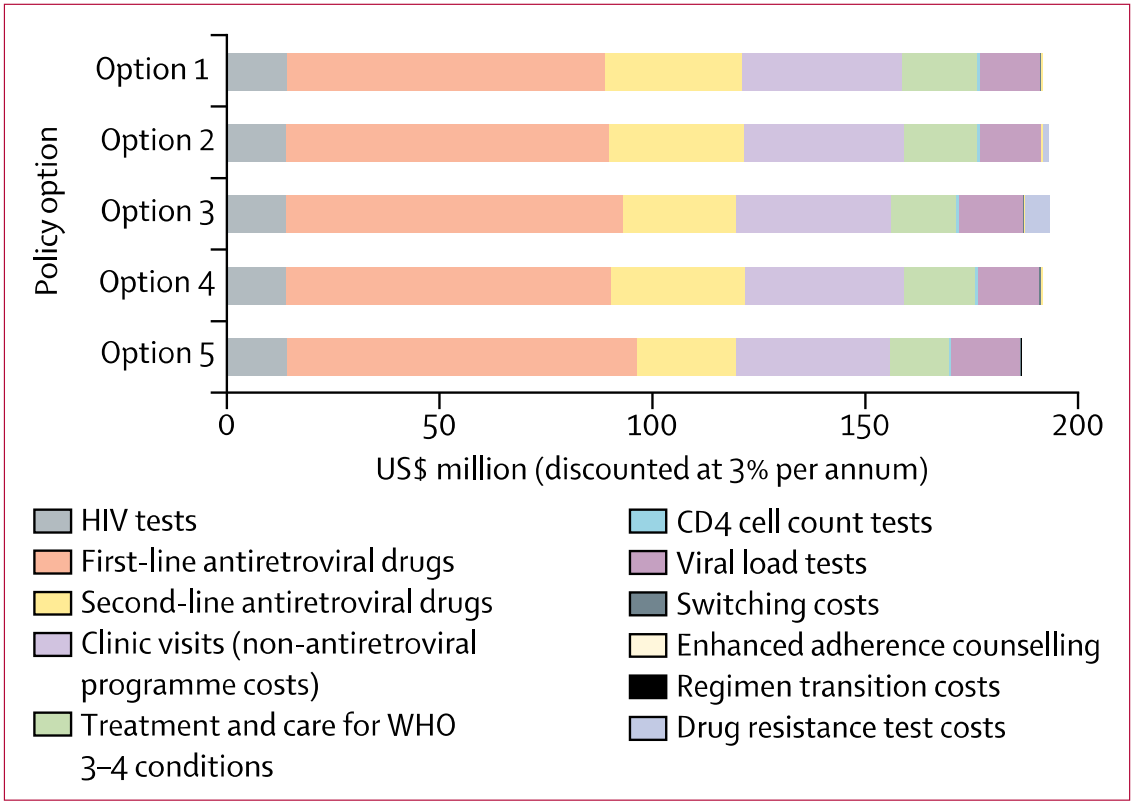
The most cost-effective option

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



A Phillips. Consultation on Global Trends of HIV Drug Resistance Rockville, Maryland, USA. May 2016

The most cost-effective option



Option 1: No change.
Option 2: DR tests for ART initiators with previous antiretroviral exposure.
Option 3: DR tests for all ART initiators.
Option 4: First-line DTG for people with previous ART exposure.
Option 5: First-line DTG for all ART initiators.

A Phillips et al. Lancet HIV 2018

The most cost-effective option

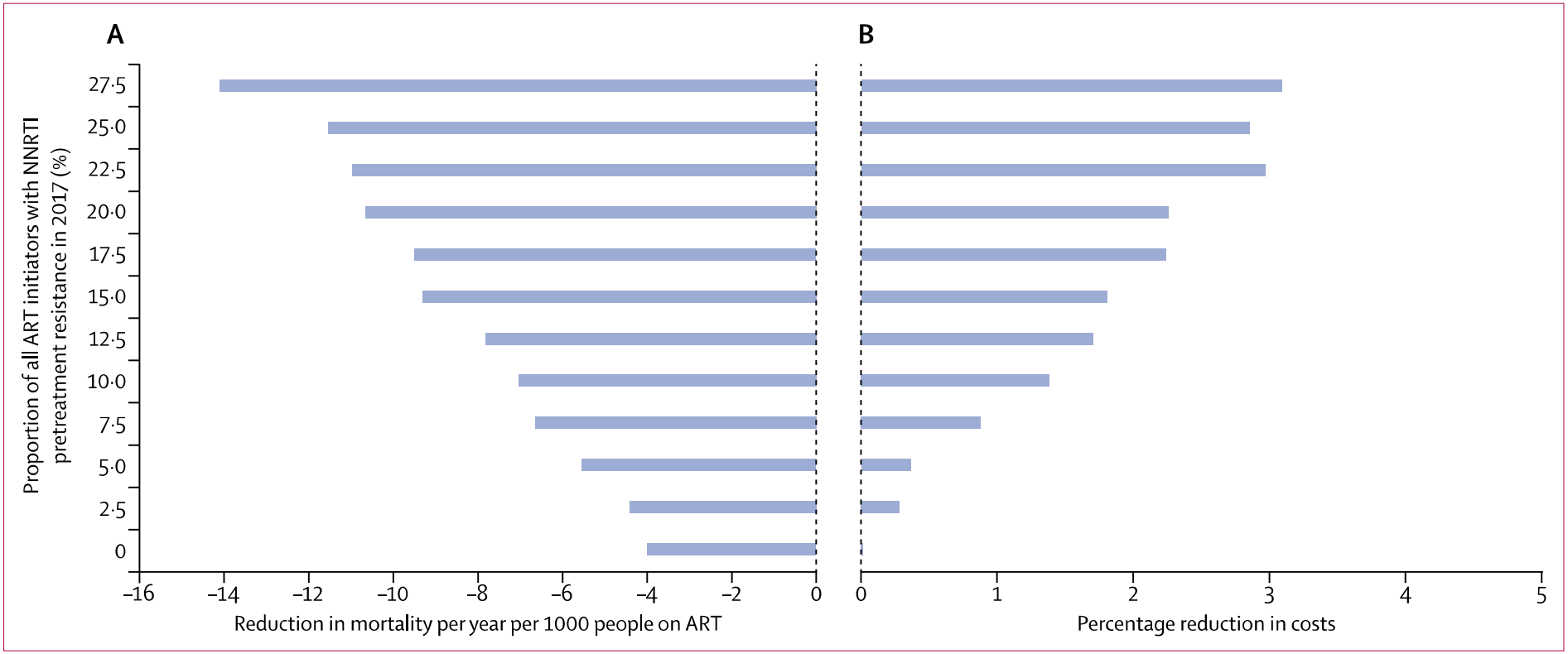


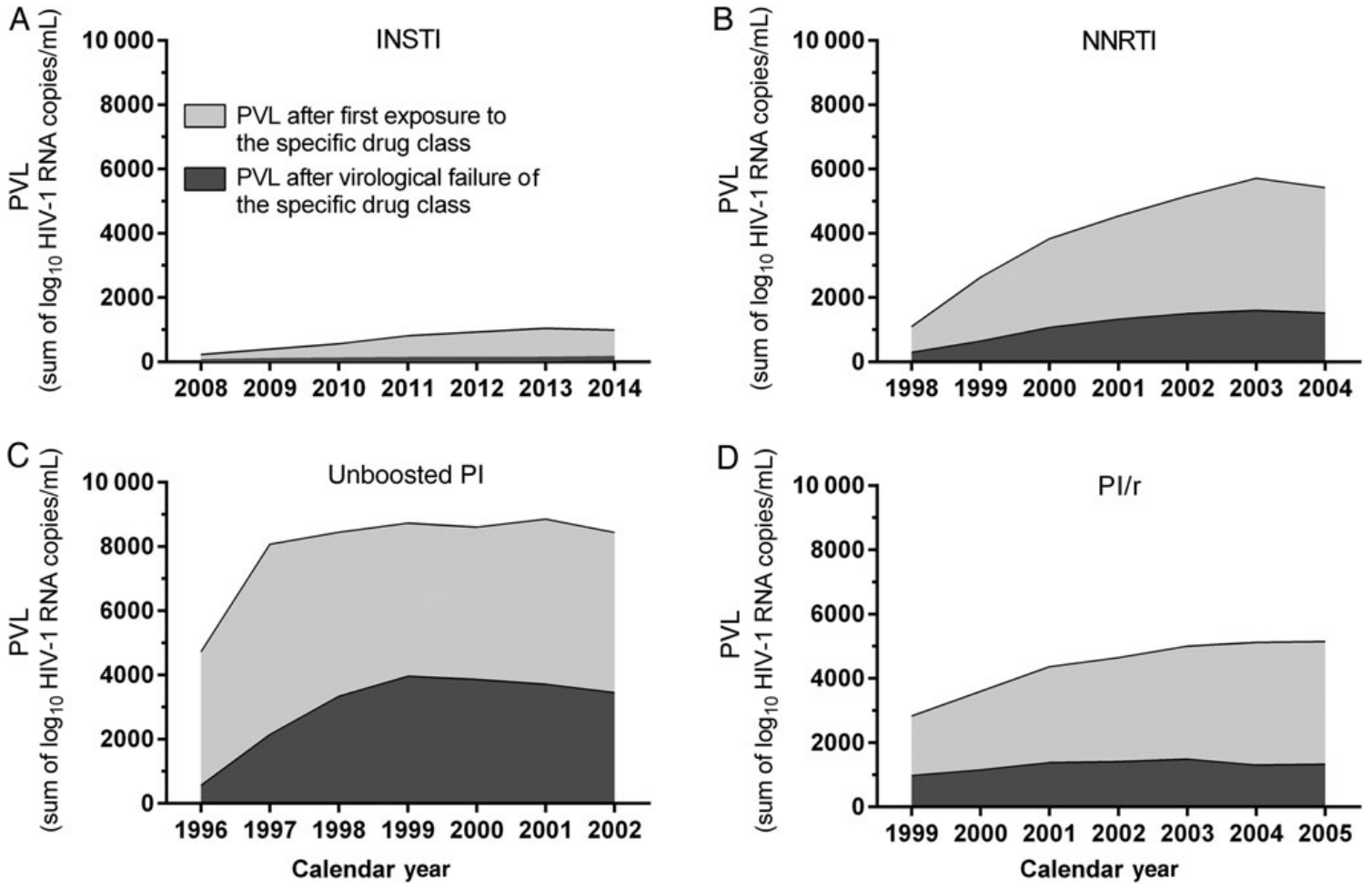
Figure 4: **Reductions in mortality and cost associated with use of dolutegravir in ART initiators rather than efavirenz**
(A) Difference in mortality (per 1000 people on ART per year) for 2018–38 when using dolutegravir in ART initiators versus continuing with efavirenz-based ART, according to proportion of all ART initiators with NNRTI resistance in 2017. 95% CIs are narrower than +/– 0·1. (B) Percentage reduction in annual costs for the policy of using dolutegravir in ART initiators versus continuing with efavirenz-based ART, according to proportion of all ART initiators with NNRTI resistance in 2017. 95% CIs are narrower than +/– 0·4. ART=antiretroviral therapy. NNRTI=non-nucleoside reverse transcriptase inhibitor.

No DTG resistance after 1st-line DTG VF in RCTs

Study	Summary efficacy	PDVF in DTG arm	INSTI resistance
FLAMINGO	DTG > DRV/r	2 / 242	0
ARIA	DTG > ATV/r	1/ 248	0 (1 K219K/Q + E138E/G)
SINGLE	DTG > EFV	18 / 422	1 E157Q/P (no emergent INSTI DR)
SPRING-2	DTG = RAL	16 / 411	0

- DTG better than non-INSTIs, non-inferior to RAL
- No INSTI resistance emergence in **ideal** conditions
  - ART-naive
  - WT virus → Active backbone
  - Early ART switch after PDFV

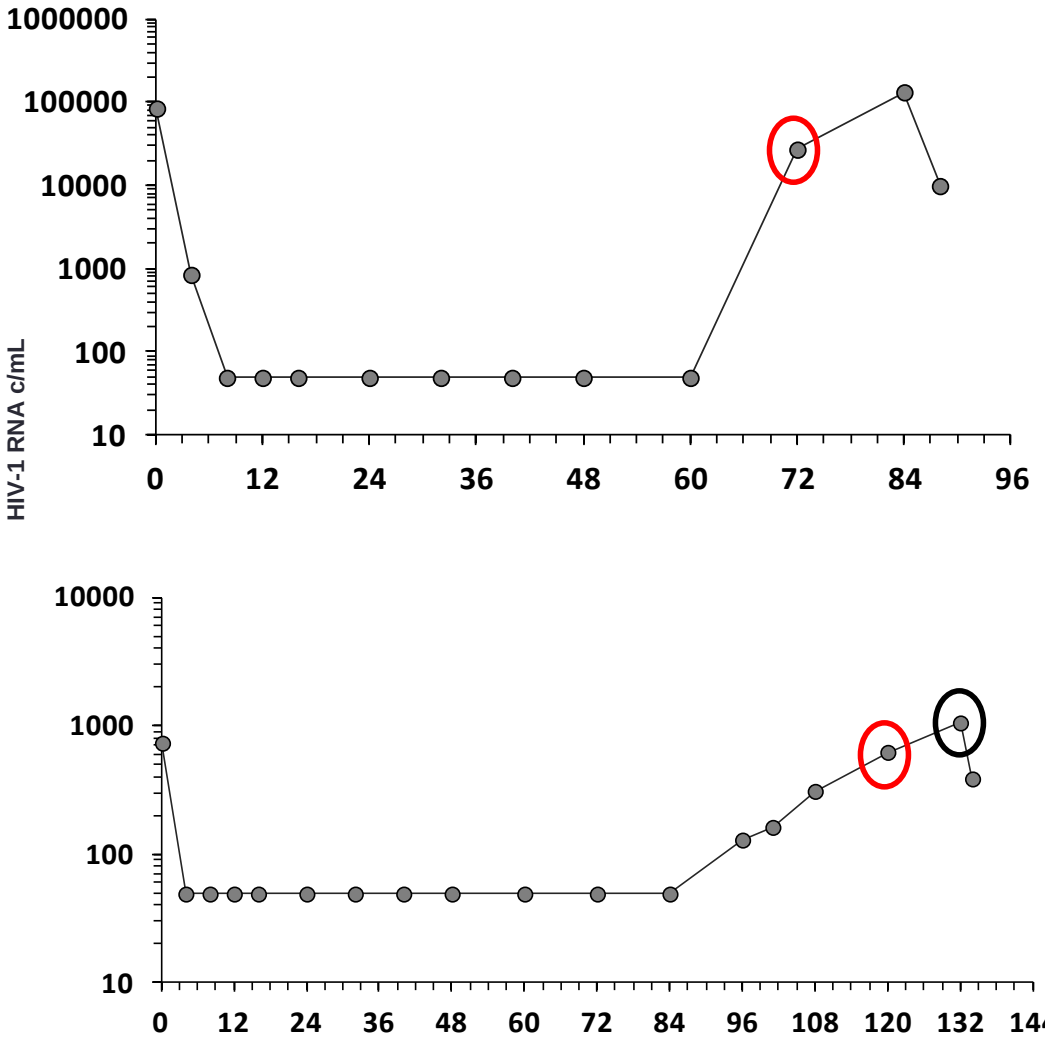
Slow resistance development and transmission in resource-rich settings



Scherrer A, et al. J Infect Dis 2017

But…

SAILING: Subjects 4 & 3



	Day 1	PDVF
HIV-1 RNA	84313	27050
IN mutation	-	I60L, T97A, N155H
DTG FC	0.66	2.4
RAL FC	0.52	113
IN RC	NR[b]	NR

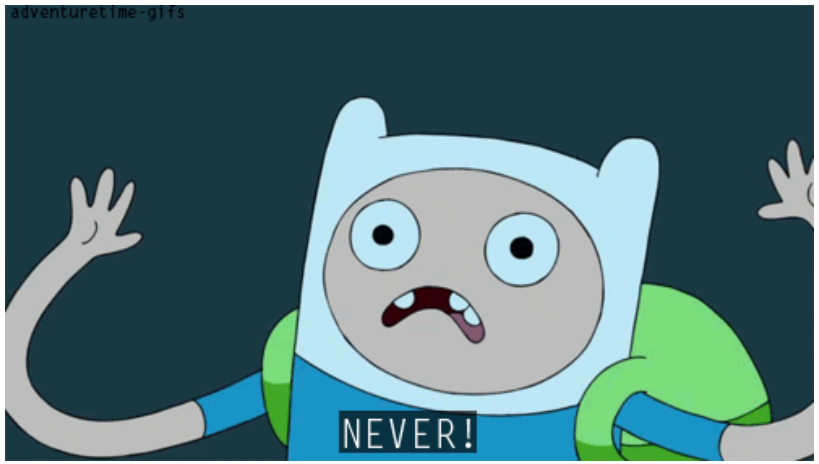
PDVF BR: No emergent resistance, loss of RT M184V and PI L10F, M36I, M46I, I54V, V82A.

	Day 1	PDVF	Confirm.
HIV-1 RNA	733	622	1054
IN mutation	-	A49G, S230R, R263K	A49G, S230R, R263K
DTG FC	0.73	3.82	5.77
RAL FC	0.54	2.39	2.62
IN RC*	20%	7.1%	12%

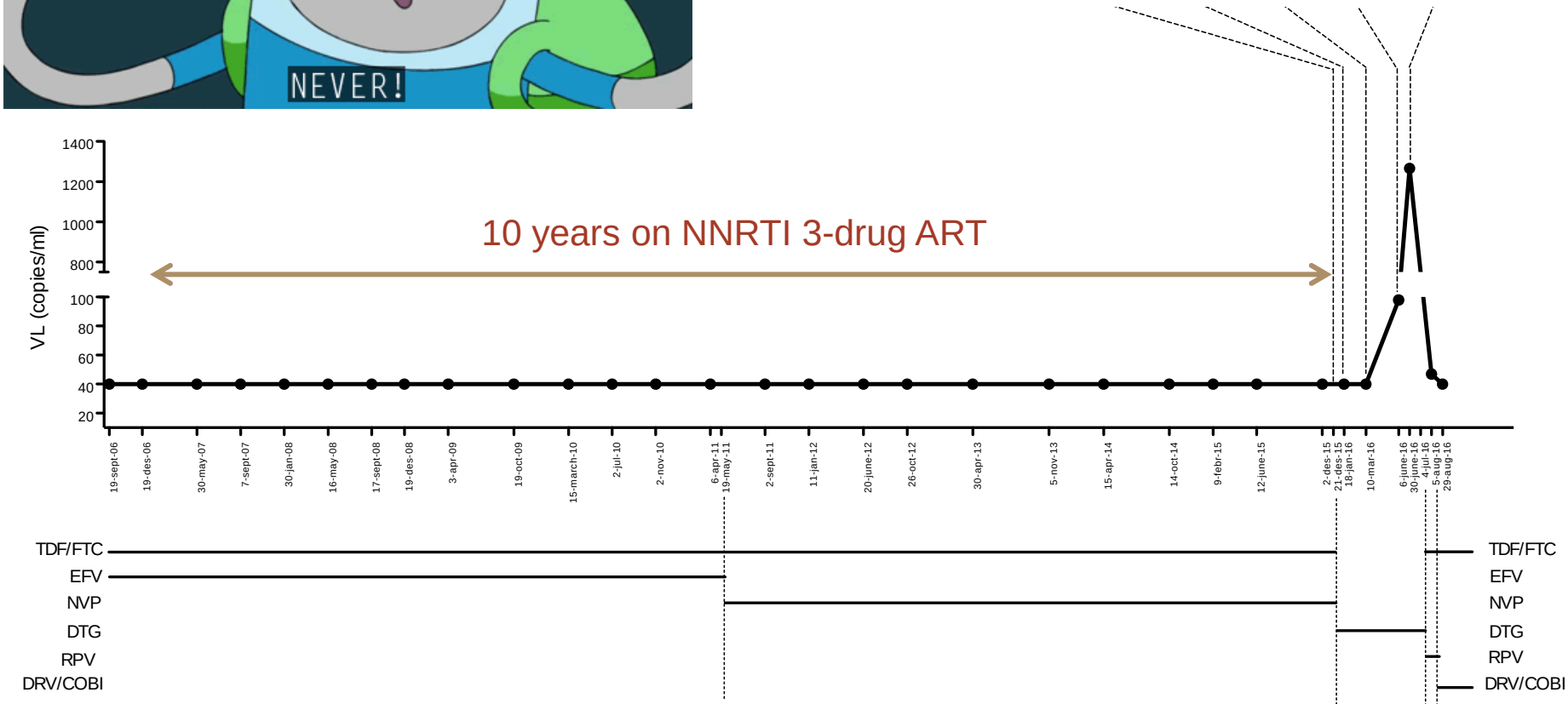
PDVF BR: No emergent resistance, and no NRTI resistance at any time points

Underwood, et al. Abs#85. IDRW June 4-8, 2013. Toronto, Canada

DTG monotherapy

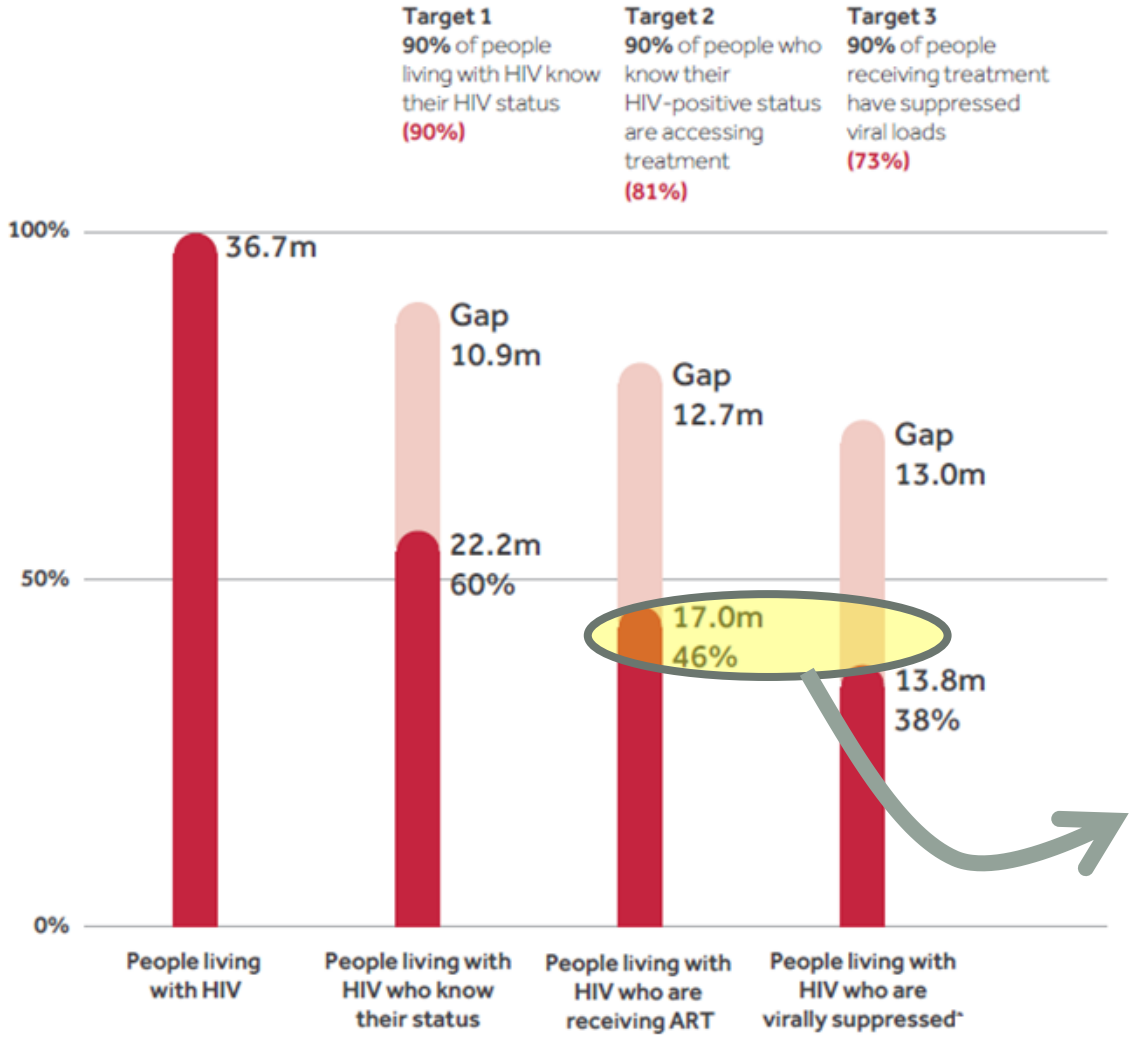


		21/12/2015	18/01/2016	10/03/2016	06/06/2016	30/06/2016
Sample Information	Study week	0	4	12	24	24 (VF confirmation)
	ART	TDF/FTC+NVP	DTG	DTG	DTG	DTG
	HIV-1 RNA	<40	<40	<40	98	1266
	Drug levels (ng/mL)					
	DTG	<LLQ	3503.916	1052.520	2899.466	-
	RAL	<LLQ	<LLQ	<LLQ	<LLQ	-
	ELV	<LLQ	<LLQ	<LLQ	<LLQ	-
	DRM by Sanger	-	-	**Plasma** RT: E138A	**Plasma** RT: E138A	**Plasma** RT: E138A
				Integrase: WT	Integrase: S147G N155H	Integrase: S147G N155H
	DRM by MiSeq	**PBMC** Pending	-	**Plasma** RT: E138A	**Plasma** RT: E138A	**Plasma** RT: E138A
				Integrase: WT	Integrase: S147G N155H	Integrase: S147G Q148R (3%) N155H



Blanco JL, et al EACS 2017

Improvements are needed at each stage of the cascade of HIV testing and treatment services, 2015

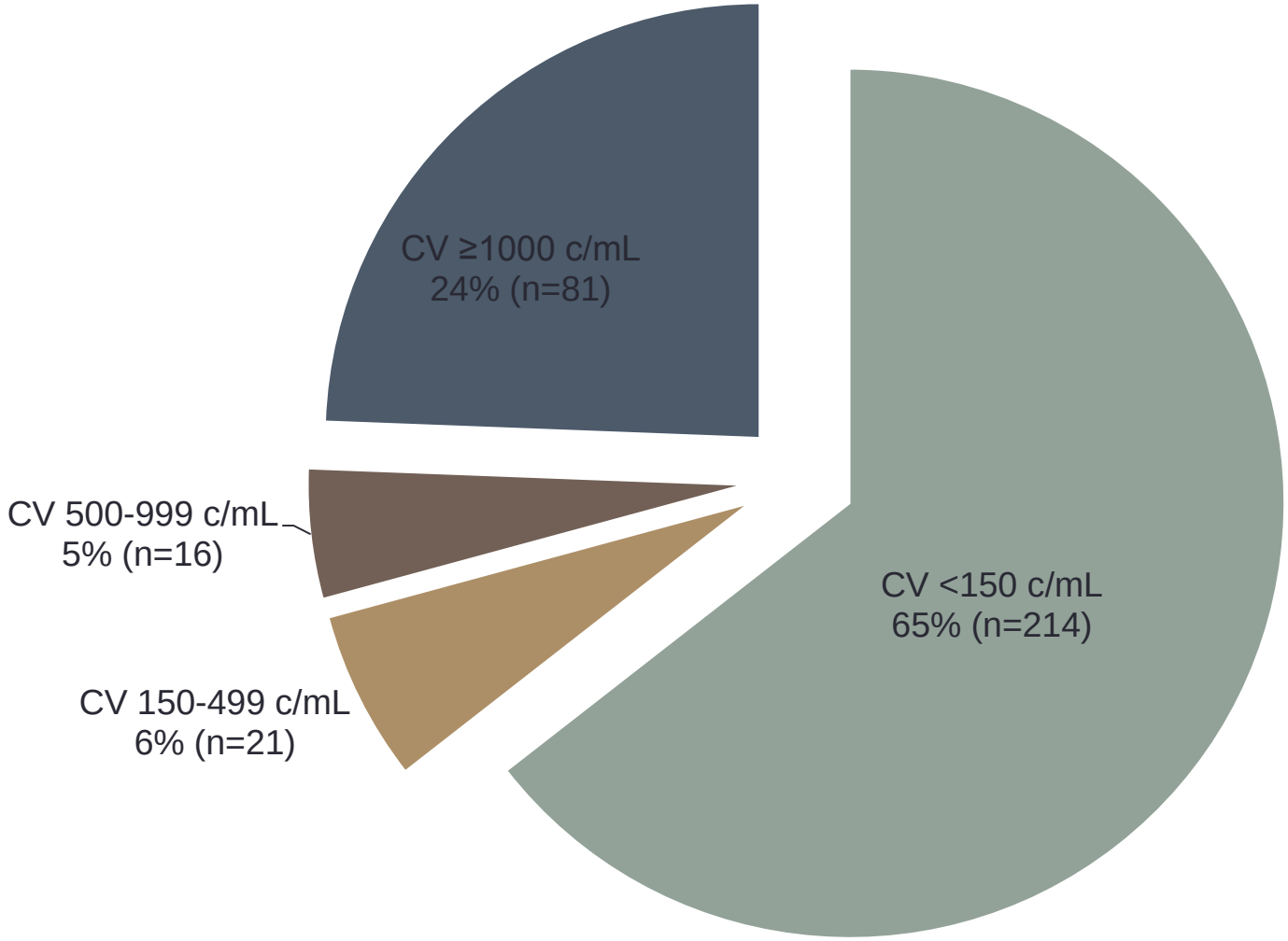


HIV drug resistance

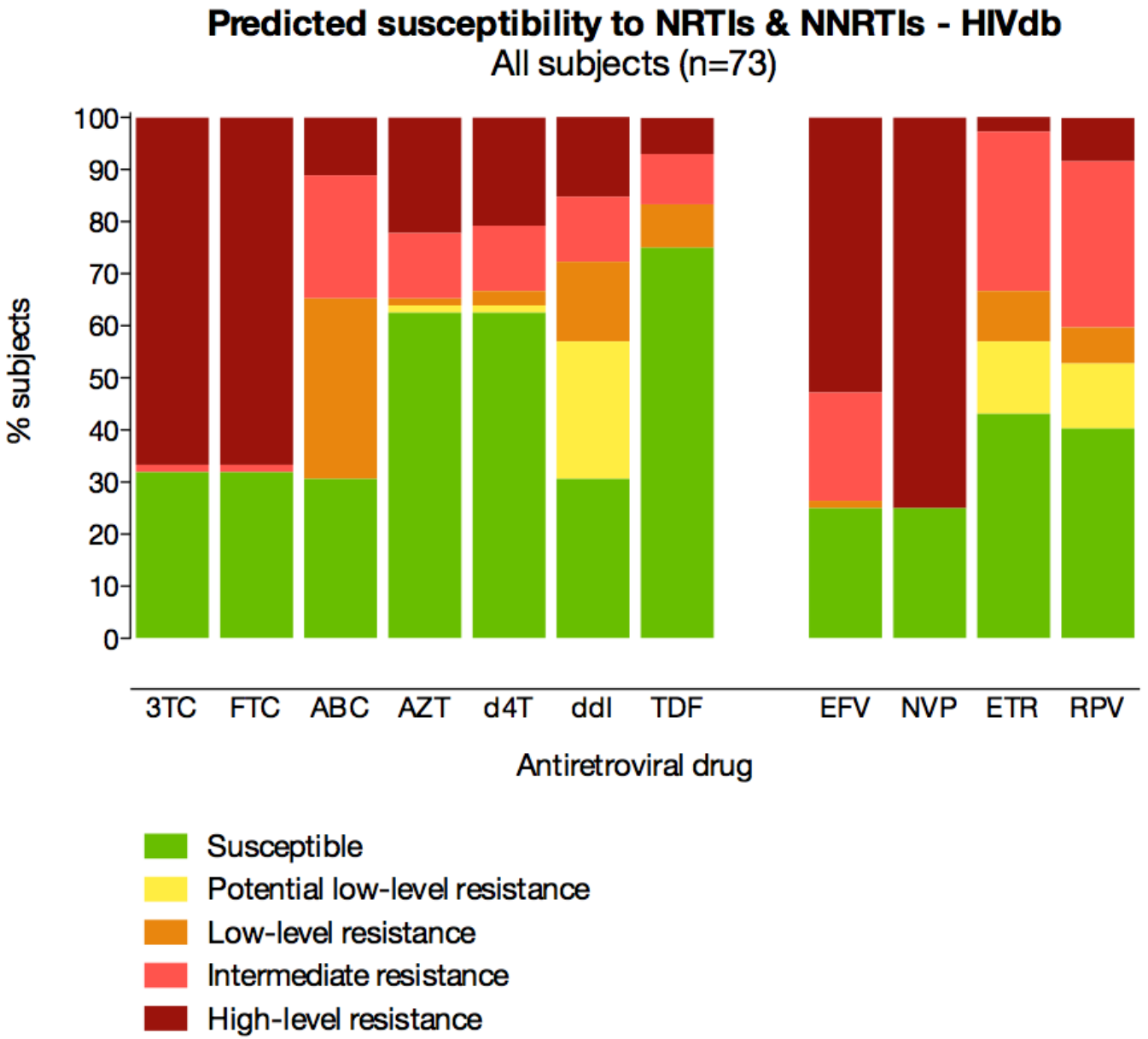
Source: UNAIDS/WHO estimates.

World Health Organization

Virological status 3 years after 1st-line ART in Manhiça with no VL monitoring, 2013

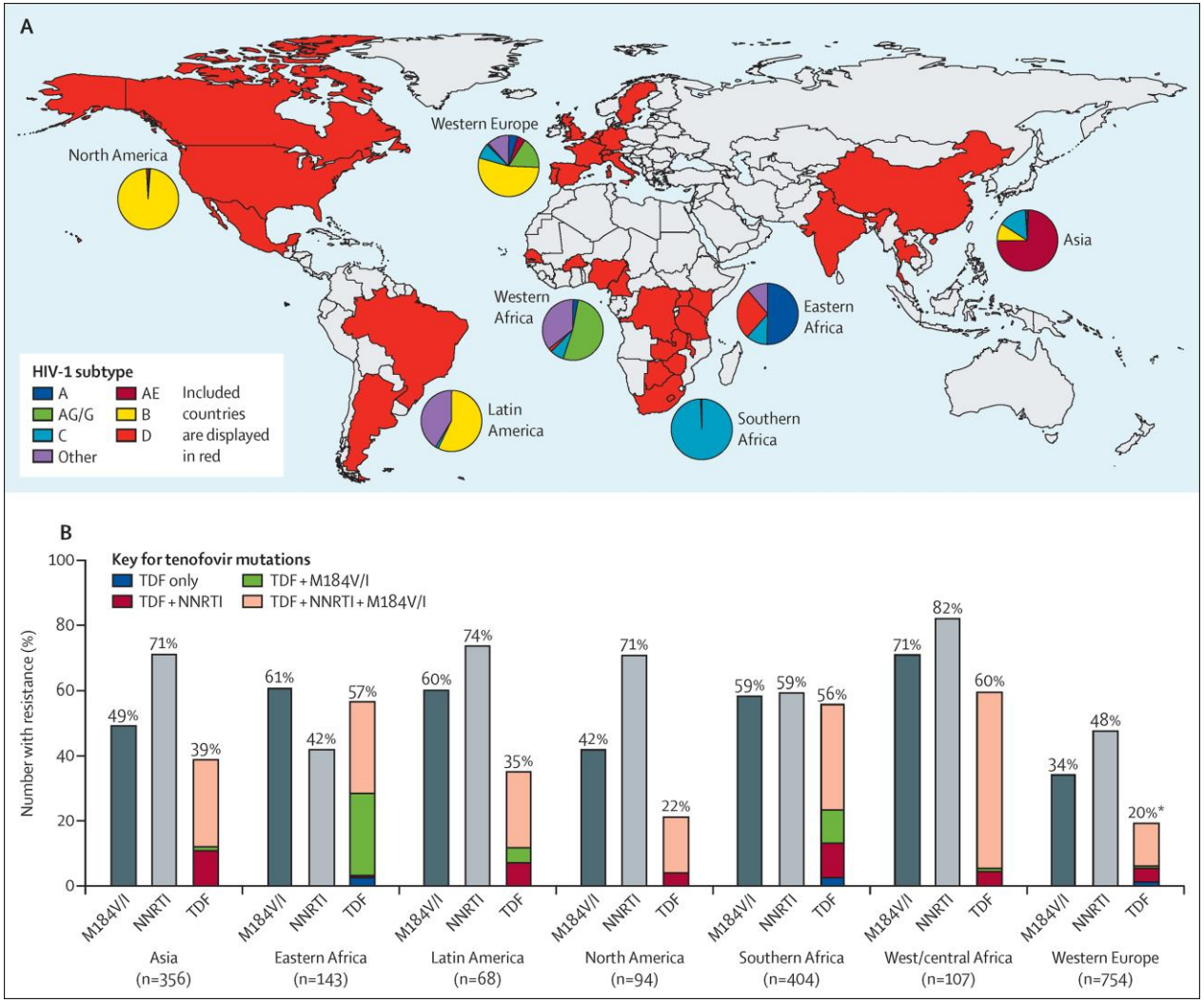


Rupérez M, JAC 2015



Rupérez M, JAC 2015

Virtual mono and dual DTG therapy



Gupta R. TenoRes Study. Lancet HIV 2016

Prevalence TDR Spain 2015-16 (n=126)

Id	Mutation	ART	CD4					HIV-1 RNA				
			0	24	48	72	84	0	24	48	72	84
1	**E138K (99.8%)**	ELV/c/FTC/TDF	988	1159	1042	-	-	172	<50	<50	-	-
2	E138K (1.4%)	DTG/ABC/3TC	51	228	246	309*	-	193297	467	274	51*	-
3	E138K (1.8%)	ELV/c/FTC/TAF	343	553	796	-	-	53388	114	<50	-	-
4	E138K (2.7%)	ELV/c/FTC/TDF	174	359	419	526	717	29166	<50	<50	68	<50
5	**R263K (99.8%)**	DTG+TDF/FTC	762	1107**	-	-	-	421000	<50**	-	-	-
6	Q148H (2.4%)	DTG+TDF/FTC	335	654	708	-	-	216232	<50	<50	-	-

(*treatment change to DRV/r+3TC/ABC (virologic) / ** treatment change to ABC/3TC/DTG)

Casadella M, et al. Europ Workshop HIV & Hep 2017

Which backbone will fit?

DTG monotherapy must be avoided

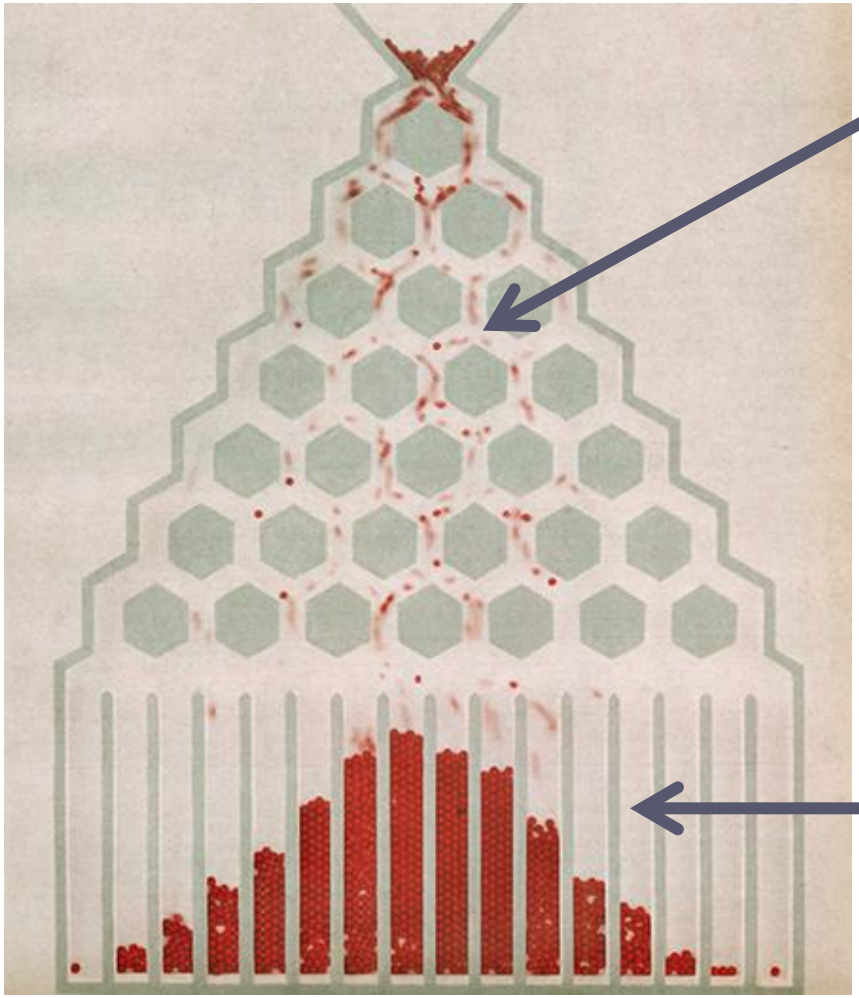
With ***Sanger Sequencing***:

- 40-70% XTC-resistant
- 35% AZT-resistant
- 60% ETR, RPV-resistant

- TDF-resistant
  - If no TDF exposure: 25%
  - If TDF exposure: 30-50% (up to 70% with NGS)

WHAT & HOW TO MONITOR?

Public health vs. personalized approaches



Personalized med

- ***Diagnostics-based*.**
  - Cares about the fate of each individual before it has occurred
  - Tries to change it through tailored therapeutics
  - Goal: ***maximizing individual outcomes***

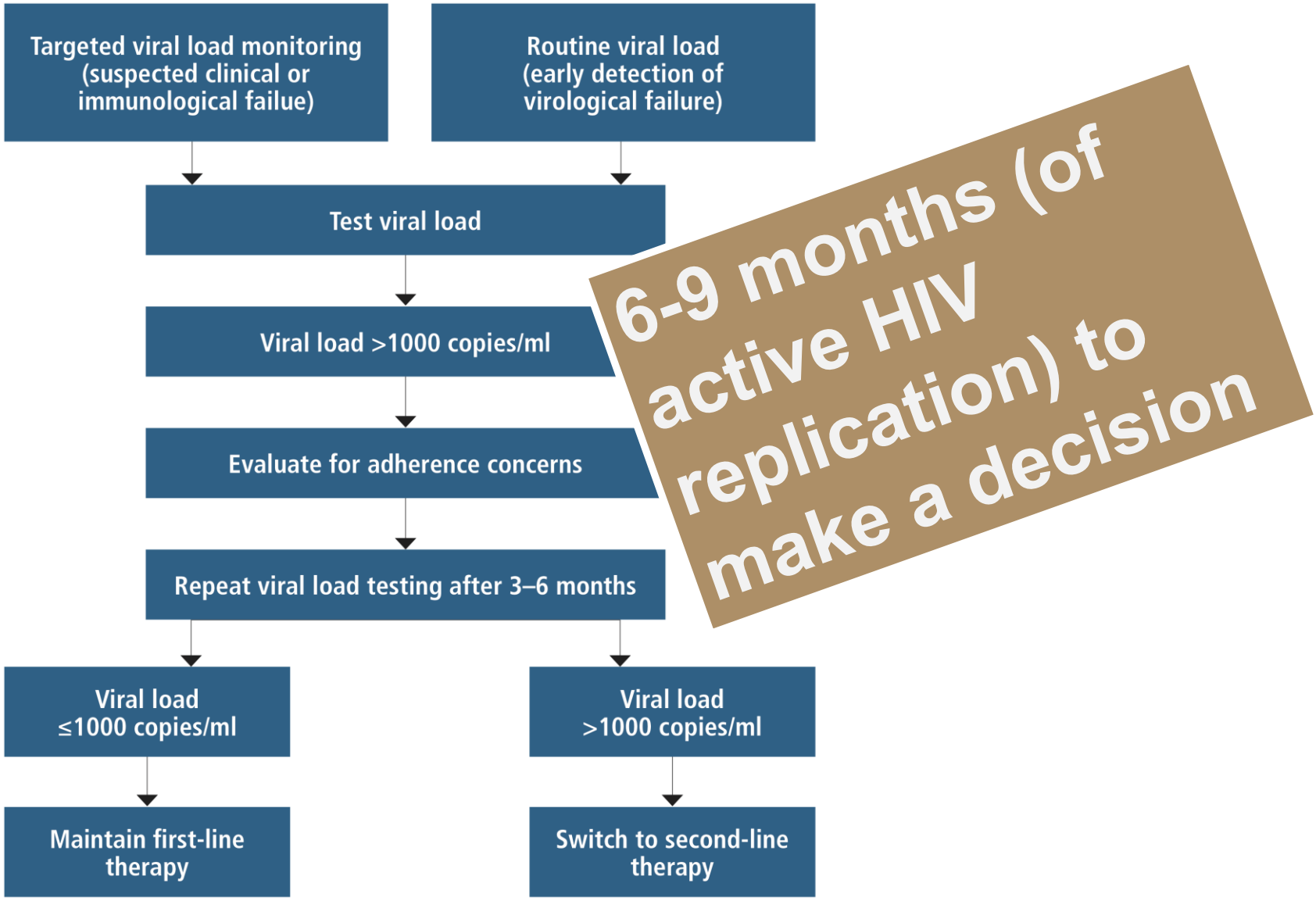
Public Health Appro

- ***Epidemiology-base***
  - cares about the population
  - Applies general rules to everyone
  - Goal: ***maximizing population outcomes by reaching more people***

DRT for clinical management

DRM surveillance

Fig. Viral load testing strategy



When is resistance testing needed for patient management?

	DTG available DTG-based ART	DTG not available EFV-based ART
Before ART	✗ No DTG PDR, rare TDF/3TC PDR	✔ If NNRTI PDR >10%
After 1st-line VF	✔ Can we continue DTG? **Is backbone resistance selected? Does it matter?**	✗ Everyone on bPI, **backbone resistance does not matter**
After 2nd-line (bPI) VF	✔ Defining a 3rd-line regimen **Any role for RAL, really? Can we recycle DTG along bPI?**	✔ Defining a 3rd-line regimen **Role for RAL/DTG**
HIV-1 infection in PrEP users	✗ ? Significant risk of TDF/3TC resistance, but, **does that matter?**	✔ High risk of TDF/3TC resistance, which is **assumed to affect the efficacy of EFV-based ART**

When is resistance testing needed for patient management?

	DTG available DTG-based ART	DTG not available EFV-based ART
Before ART	✗ No DTG PDR, rare TDF/3T…	
After 1st-line VF		…g a 3rd-line regimen **Role for RAL/DTG**
	…TG along bPI?	
…ction in PrEP users	✗ ? Significant risk of TDF/3TC resistance, but, **does that matter?**	✔ High risk of TDF/3TC resistance, which is **assumed to affect the efficacy of EFV-based ART**

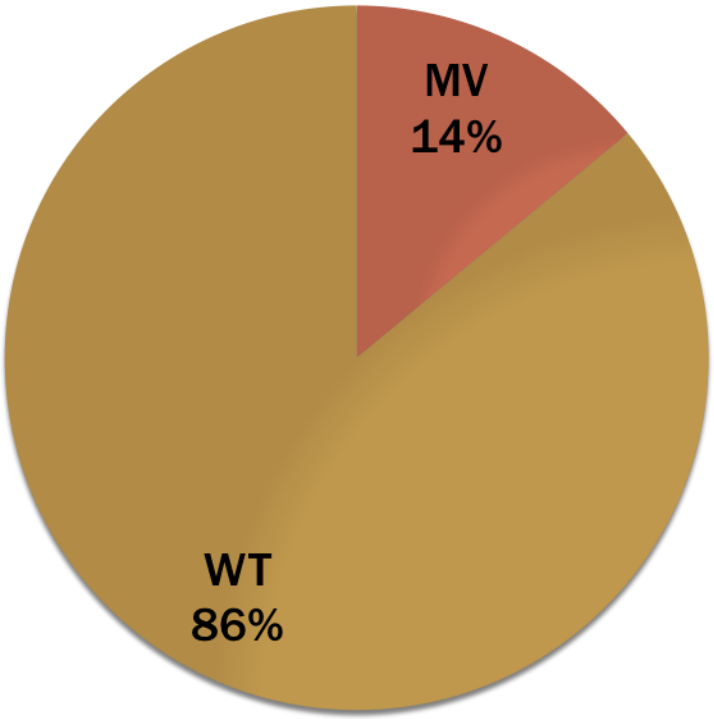
Integrase DRT is needed

For surveillance, everywhere

To manage patients, where DTG is available

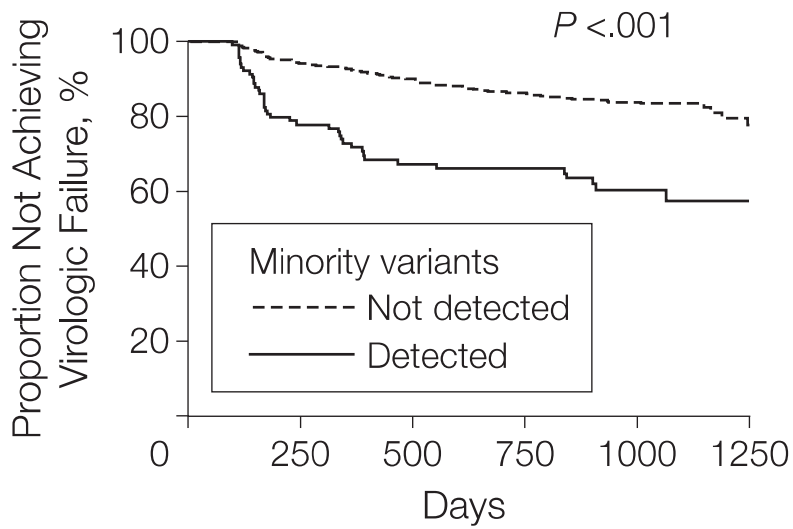
Importance of the NRTI backbone

NNRTI DRM in ART-naive



Number needed to test: 11

Figure 2. Kaplan-Meier Curves for Proportion of Patients Without Virologic Failure by Presence of Drug-Resistant HIV-1 Minority Variants

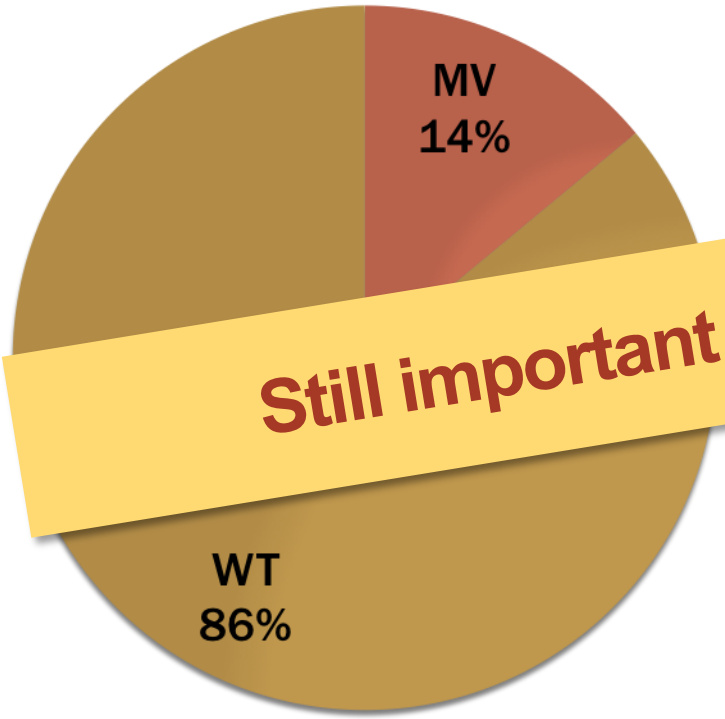


No. at risk

Minority variants						
Not detected	691	620	455	398	344	46
Detected	117	86	60	53	37	7

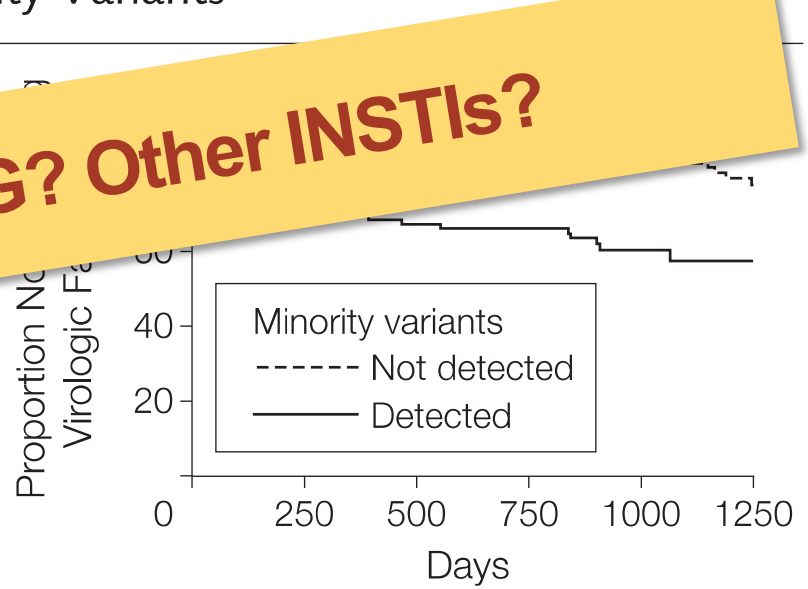
Li J et al. JAMA 2011

NNRTI DRM in ART-naive



Still important for DTG? Other INSTIs?

Figure 2. Kaplan-Meier Curves for Proportion of Patients Without Virologic Failure by Presence of Drug-Resistant HIV-1 Minority Variants



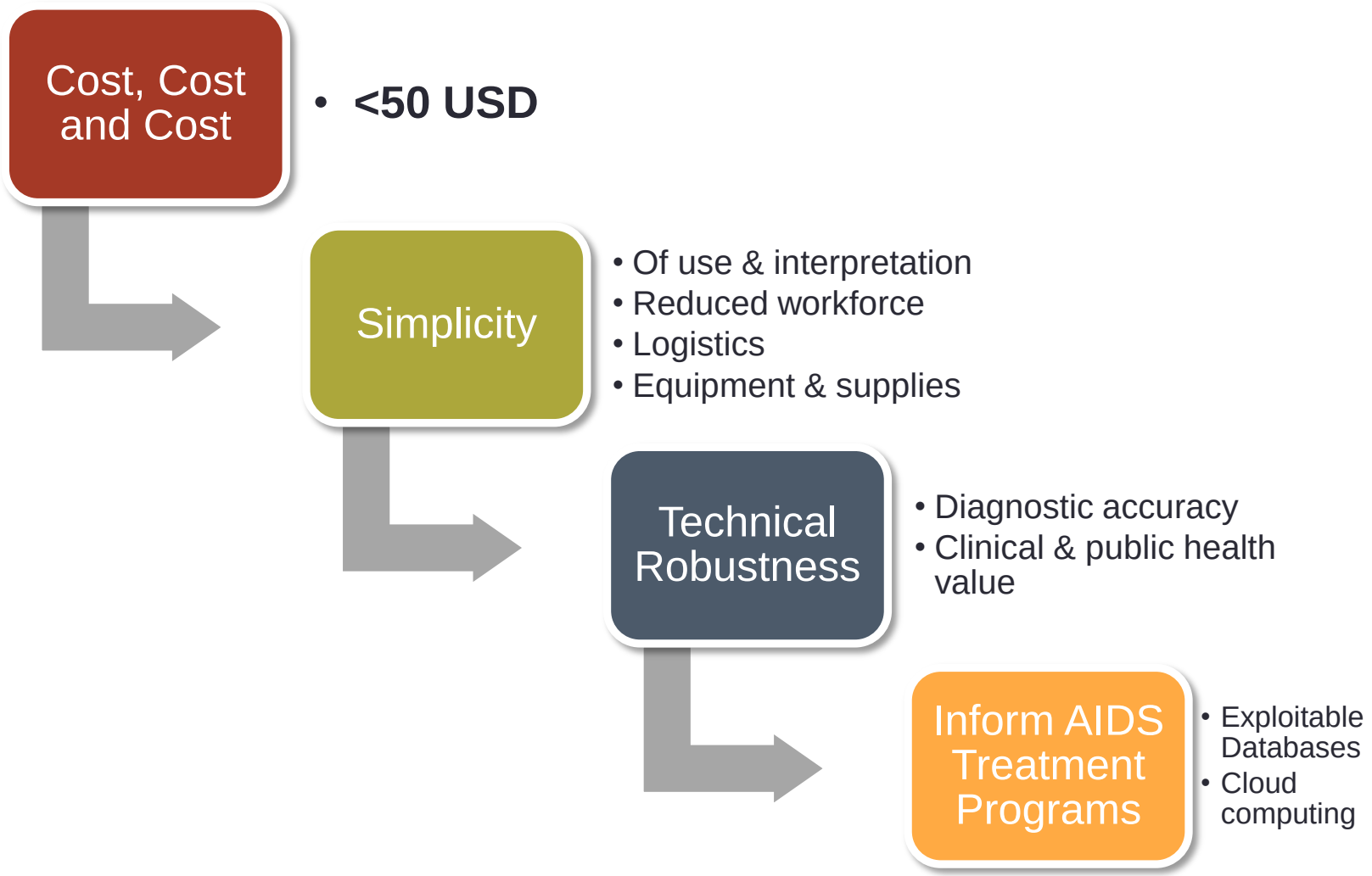
No. at risk						
Minority variants						
Not detected	691	620	455	398	344	46
Detected	117	86	60	53	37	7

Number needed to test: 11

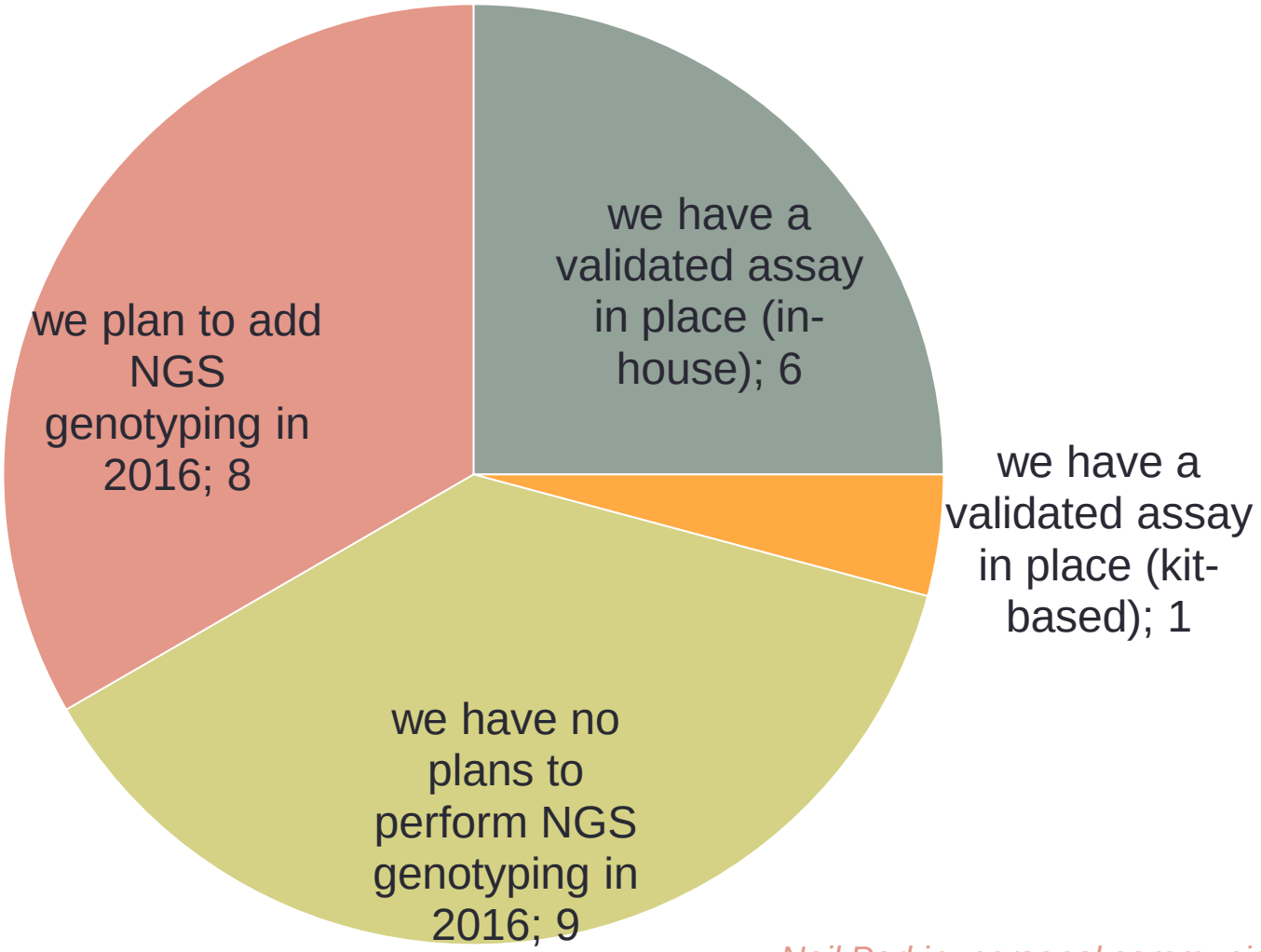
Li J et al. JAMA 2011

Which technique?

Priorities for new resistance technologies



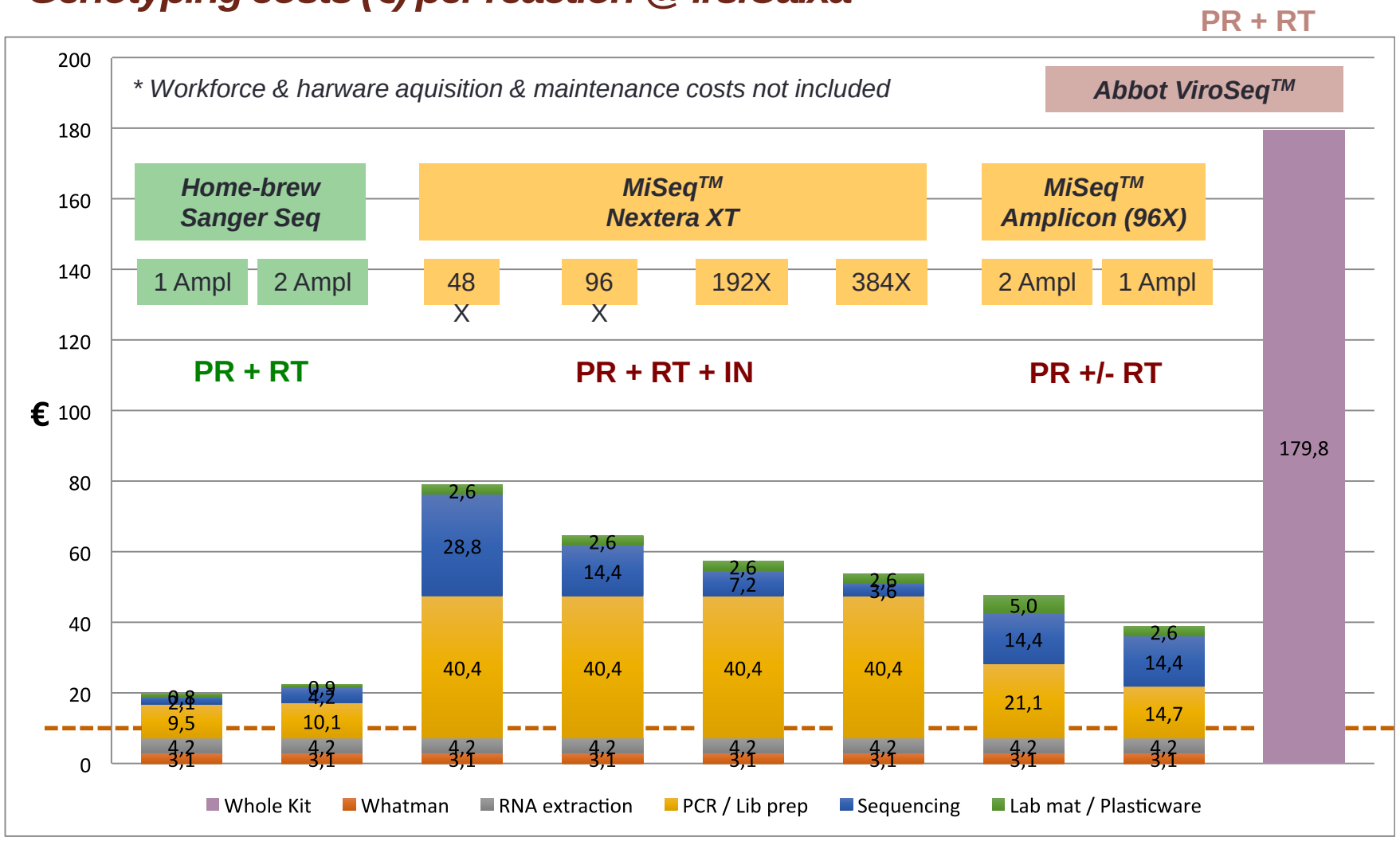
NGS in the WHO-acredited labs 2016



Neil Parkin, personal communication

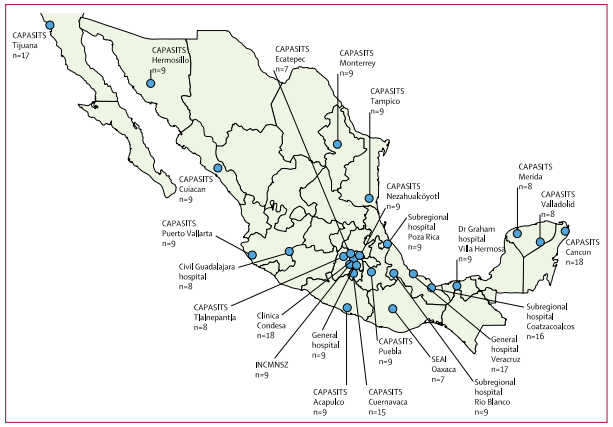
Operational challenges: Sequencing costs

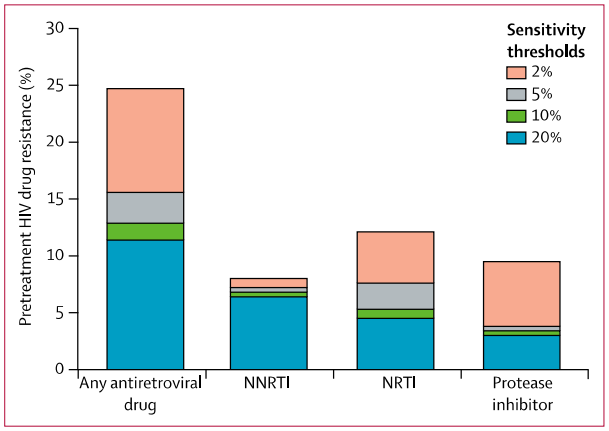
Genotyping costs (€) per reaction @ irsiCaixa

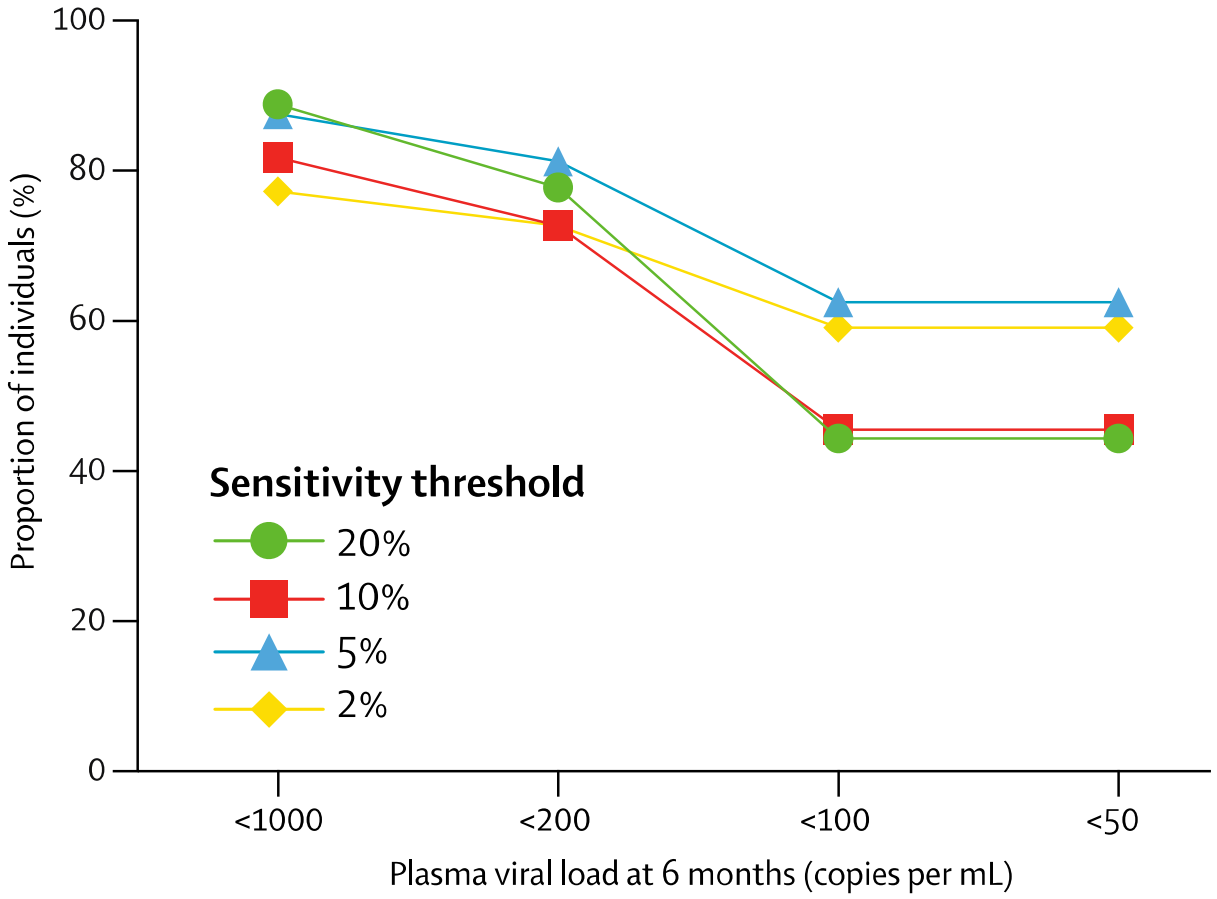


--- GeneXpert MTB/RIF: 9.98 US$ / test

What is the NGS cutoff? 5%?

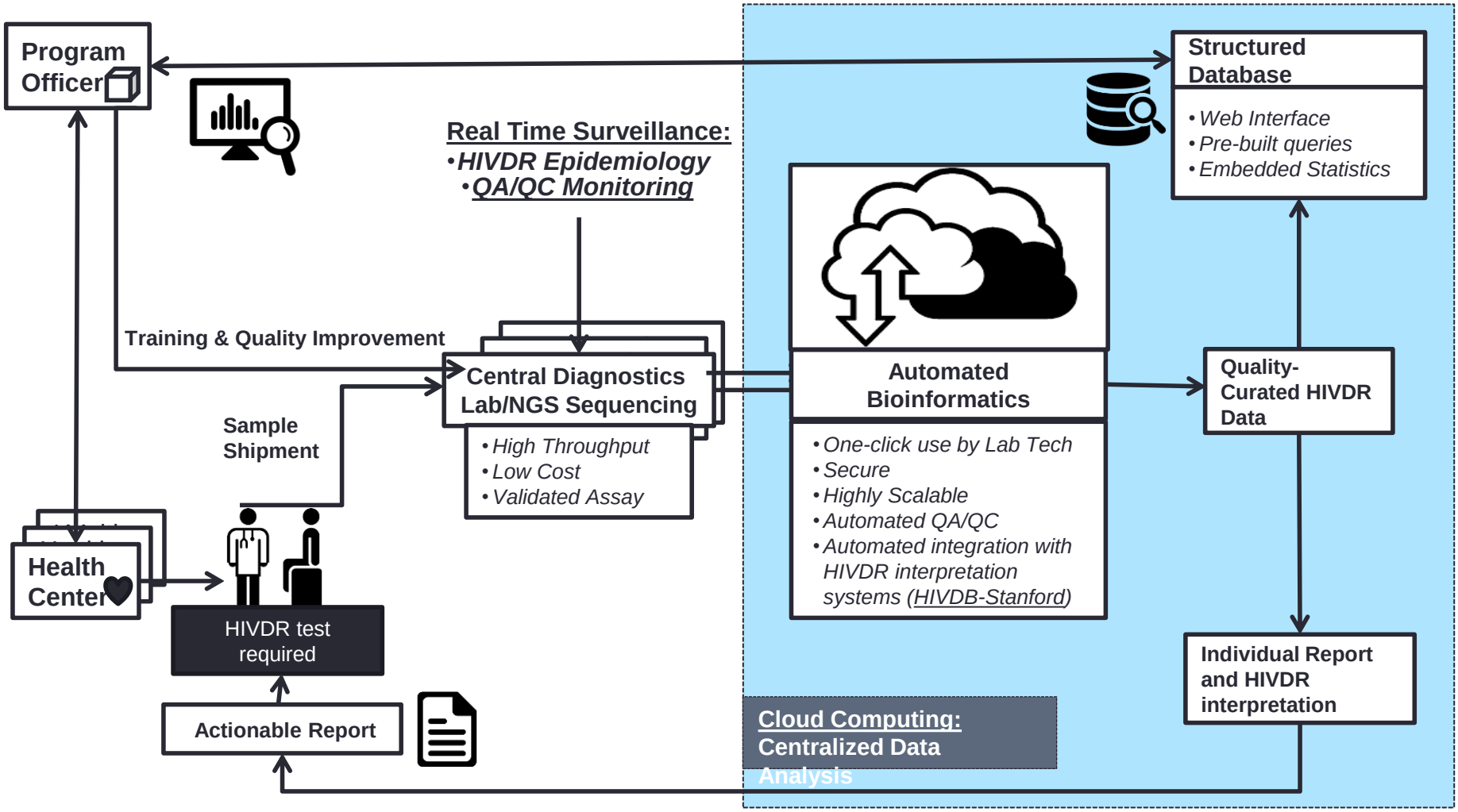






Avila-Rios et al. Lancet HIV 2016

Integrated NGS cloud computing for real-time surveillance

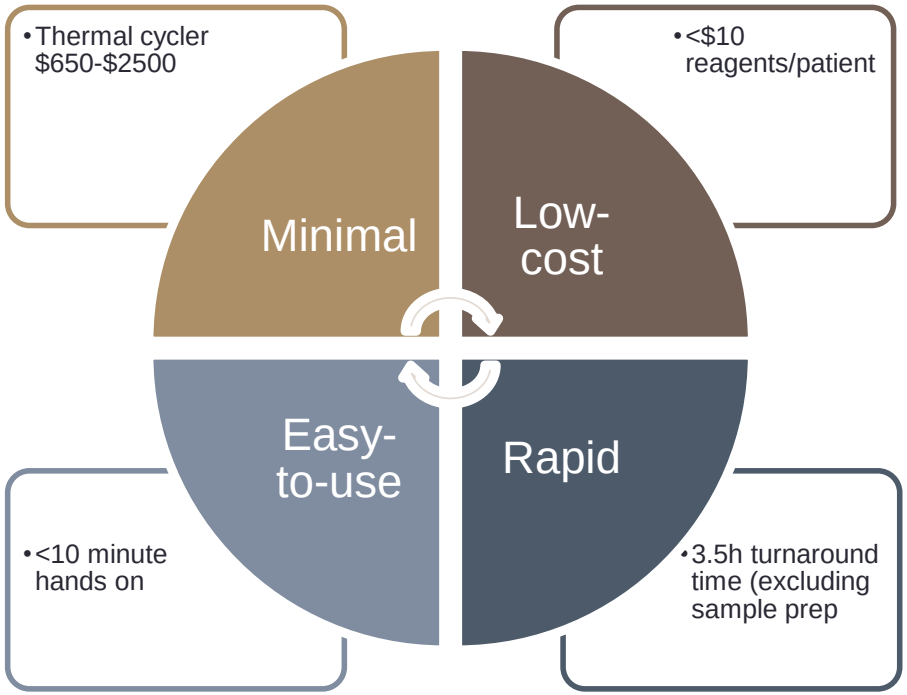


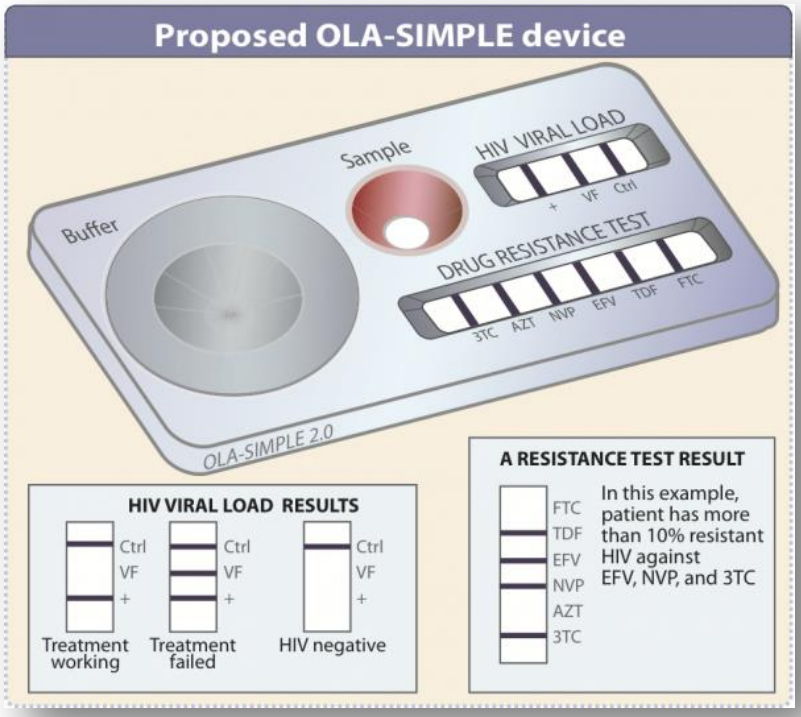
Noguera-Julian M. J Infect Dis 2017

PASeq (paseq.org)

Noguera-Julian M, et al. J Infect Dis 2017

Oligonucleotide Ligation Assay (OLA)

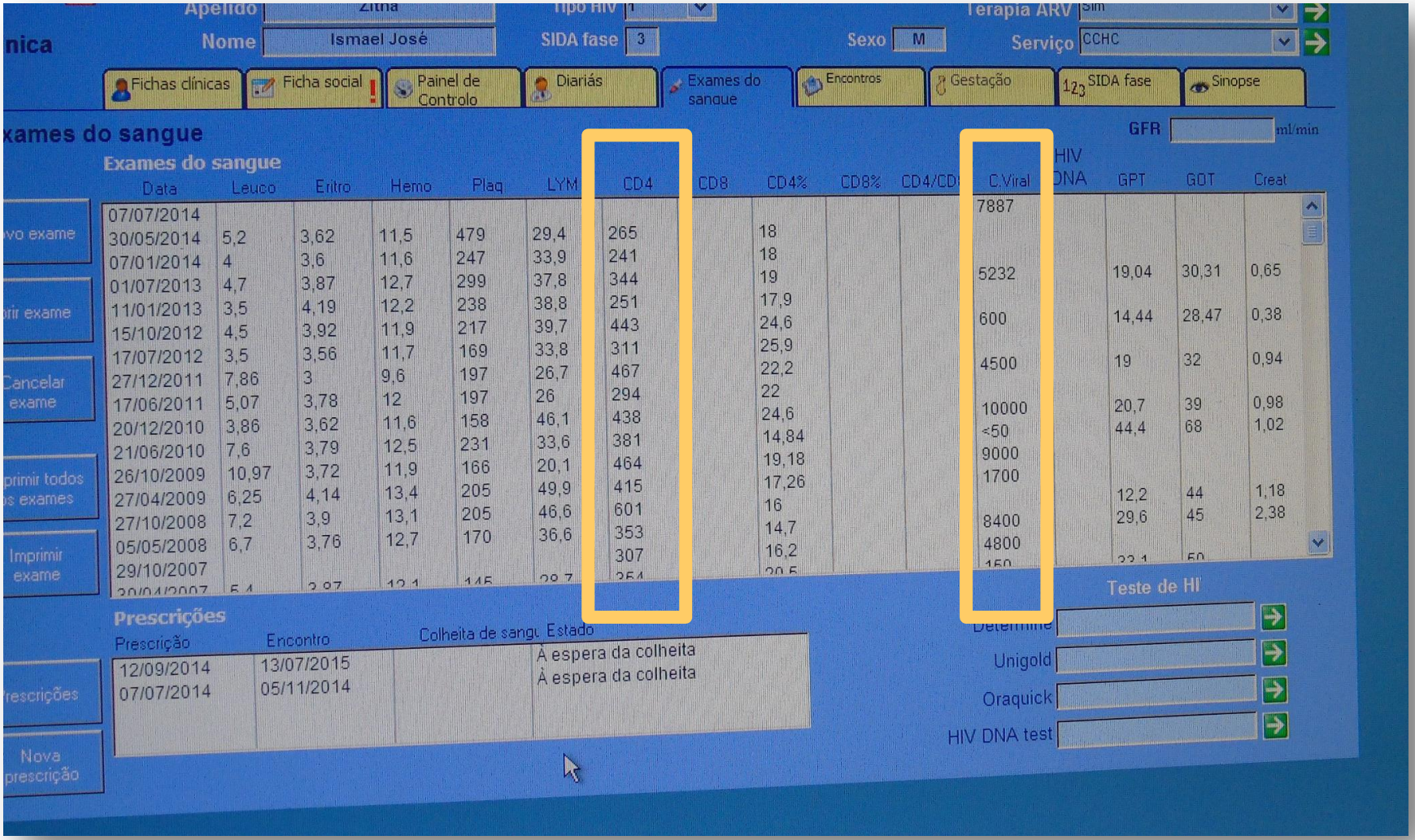




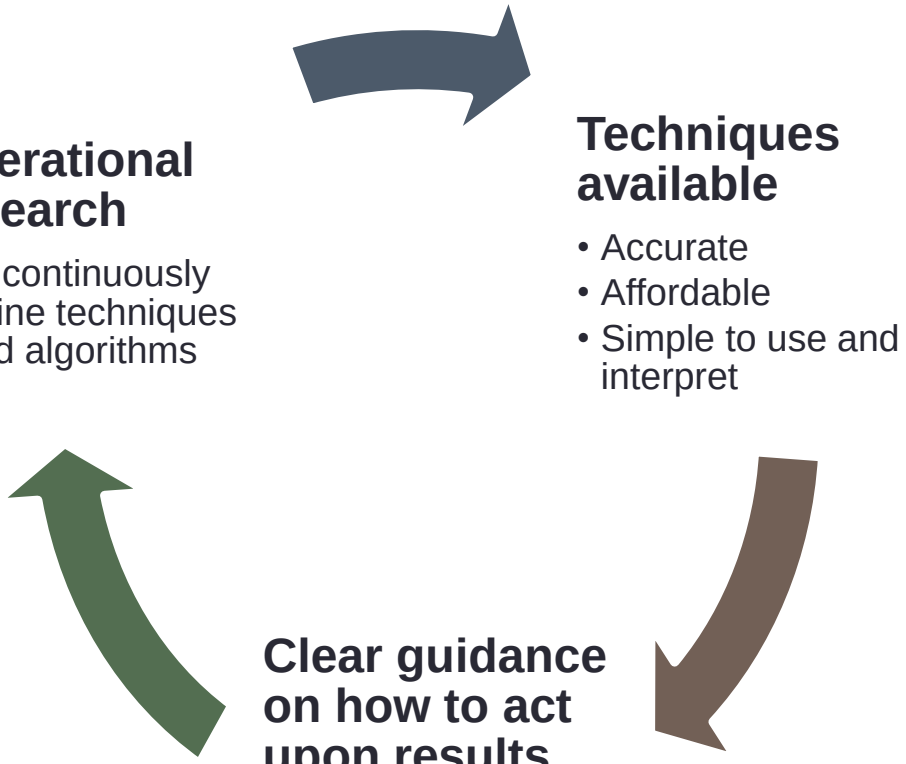
Panpradist N, et al. PLoS One 2016

Highly simplified NGS sequencers

Challenges to implementation



Techniques must be embedded with guidance



HIV Drug Resistance: 2018 Review and Recommendations of The International Antiviral Society-USA Panel

Huldrych F. Günthard, MD; Vincent Calvez, MD; Roger Paredes, MD; Deenan Pillay, MD; Robert W. Shafer, MD; Annemarie M. Wensing, MD; Donna M. Jacobsen, BS; Douglas D. Richman, MD

CID 2018 under review

Transmission of Minority Variants Harboring DRMs

- Both NGS & Sanger equally useful
- Drug resistance testing to detect minority variants is not currently recommended outside of research settings but may be considered for NNRTIs (evidence rating AIIa).
- NGS must report
  - Always: Sanger-like cut-off (15%)
  - Optional 5% (NNRTIs)
  - Store info down to 1%

Integrase testing

- Routine InSTI resistance testing in drug naive individuals is currently not recommended (BIII)
- Baseline InSTI resistance testing is recommended in select patients with evidence of TDR, such as those with nRTI- or multi-class resistance (evidence rating AIII).
- Monitoring of TDR/PDR to InSTI in selected sites in resource rich- and in LMIC-settings is recommended (evidence rating AIII).

Conclusions – clinical & public health implications of widespread DTG

- **ART-naive**
  - High efficacy expected → Cost-effective (& possibly life-saving) strategy
  - Efficacy with a compromised backbone?
- **ART-experienced**
  - ***INSTI - naive***
    - It's all about the backbone
    - Never DTG monotherapy
    - DTG + 3TC not suited for salvage ART (maintenance?)
    - ***DTG + bPI vs. DTG + TXF + XTC***
  - ***DTG-experienced***
    - Prior resistance testing is mandatory
    - Uncertain additional role for bictegravir → **Main problem RIF interaction**
  - ***RAL-experienced, but DTG-naive***
    - Ideally with prior genotype

Conclusions - technical

	Today	In the coming 5 years
Technique	**In-house Sanger**	**NGS + Integrated Cloud computing**, but requires: • Further cost reductions (library preparation) • Wet-lab procedures automatized **POC**, but requires further implementation research
Interpretation	Operator-driven	Automatized + supervision
Model	Decentralised	Decentralised / Distributed only if POC available
QA/QC	Hierarchical	Supervised, Real-time, Cloud-based
ART	Public health	Public Health / Personalised
Computing	+	+++

Gràcies!

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Vall d'Hebron: Manel Crespo, Jordi Navarro, Ariadna Torrela
UVIC-UCC: Malu Calle

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