HIV Drug Resistance Report 2012

Silvia Bertagnolio, MD

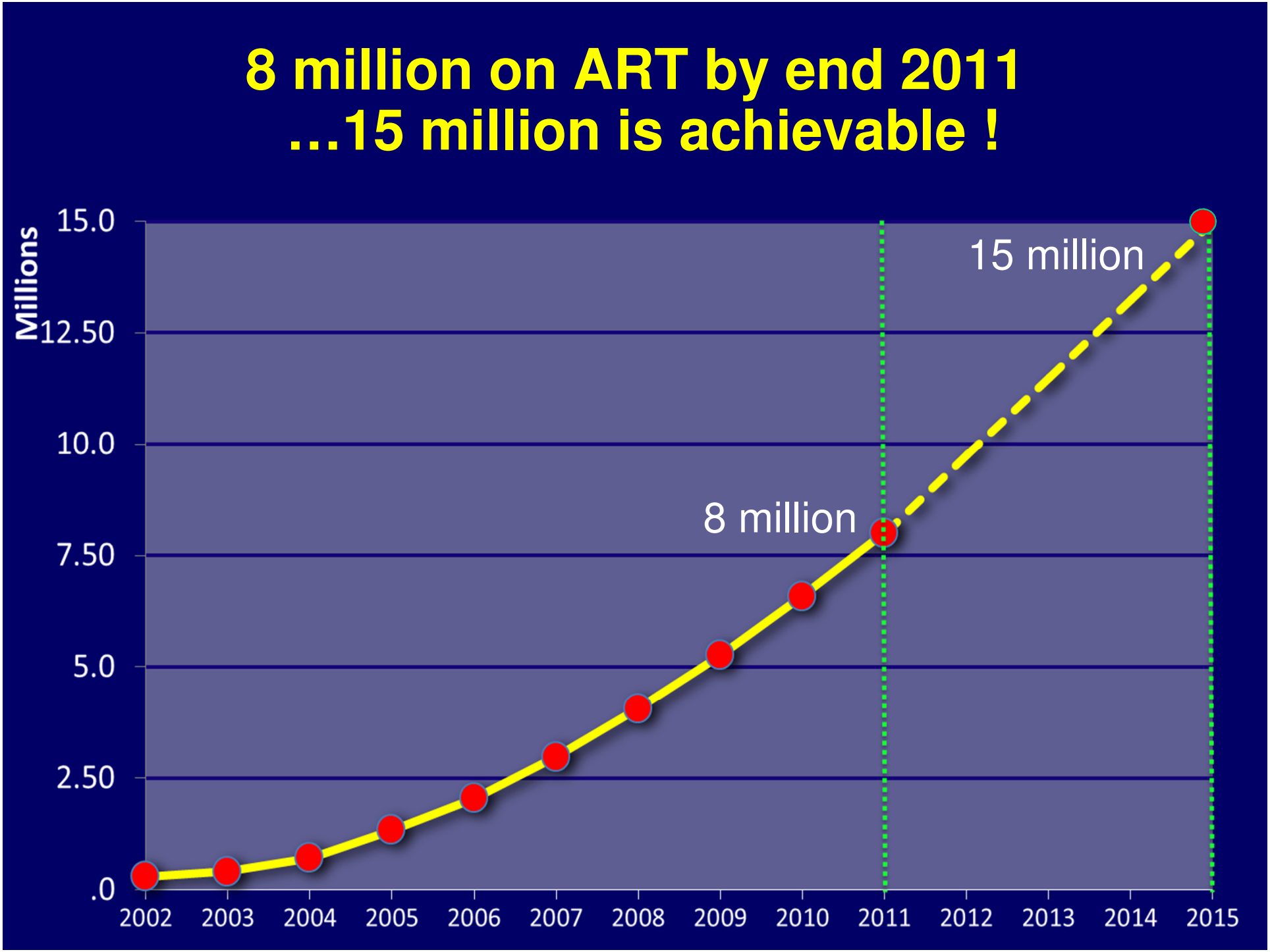
Department of HIV/AIDS,

World Health Organization

Geneva, Switzerland

Brazilia, March 19-21, 2013

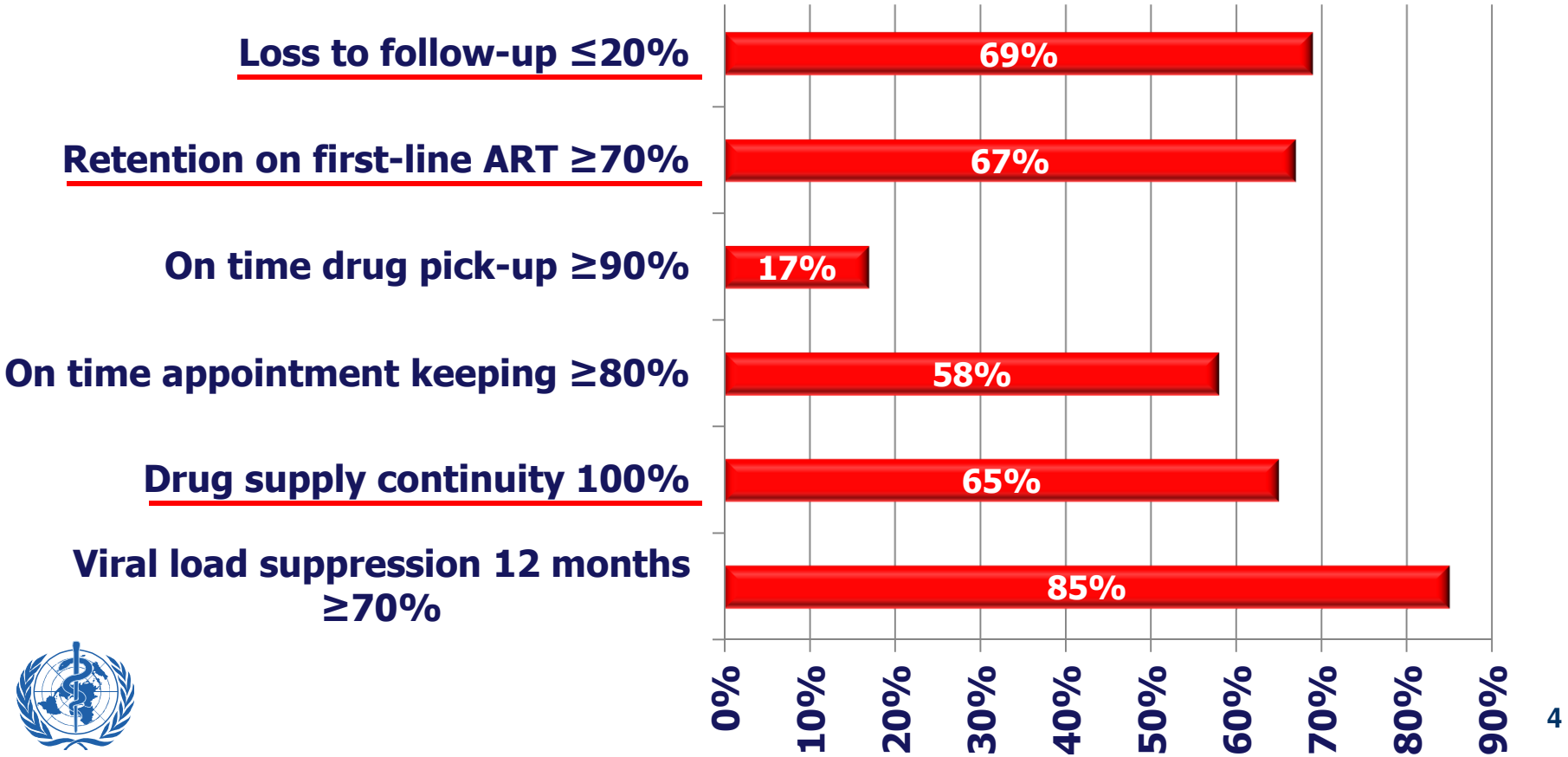
8 million on ART by end 2011
…15 million is achievable !



Scale-up of HIV prevention, treatment and care services

HIVDR early Warning Indicators (EWI) Proportion of Clinics Achieving WHO-Recommended Targets

2107 clinics (2004-2009), >131,000 people, >50 countries



Are we observing a dramatic increase in HIVDR?

VIEWPOINT

Preventing antiretroviral anarchy in sub-Saharan Africa

A D Harries, D S Nyangulu, N J Hargreaves, O Kaluwa, F M Salaniponi

Combination antiretroviral therapy has dramatically improved the survival of patients living with HIV and AIDS in industrialised countries of the world. Despite this enormous benefit, there are some major problems and obstacles to be overcome.[1] Treatment of HIV-infection is likely to be lifelong.[2] Unfortunately, many HIV-infected individuals cannot tolerate the toxic effects of the drugs, or have difficulty complying with treatment which involves large numbers of pills and complicated dosing schedules. Poor adherence to treatment leads to the emergence of drug-resistant viral strains that need new combinations of drugs or new drugs altogether.

"Widespread, unregulated access to antiretroviral drugs in sub-Saharan Africa could lead to the rapid emergence of resistant viral strains, spelling doom for the individual, curtailing future treatment options, and leading to transmission of resistant virus."

- *"If compliance and careful follow-up of patients is not achieved,* ***we will see a dramatic increase in multidrug-resistant HIV mutants…"***
- *Robert C. Gallo and Luc Montagnier. Prospects for the Future. Science 2002*

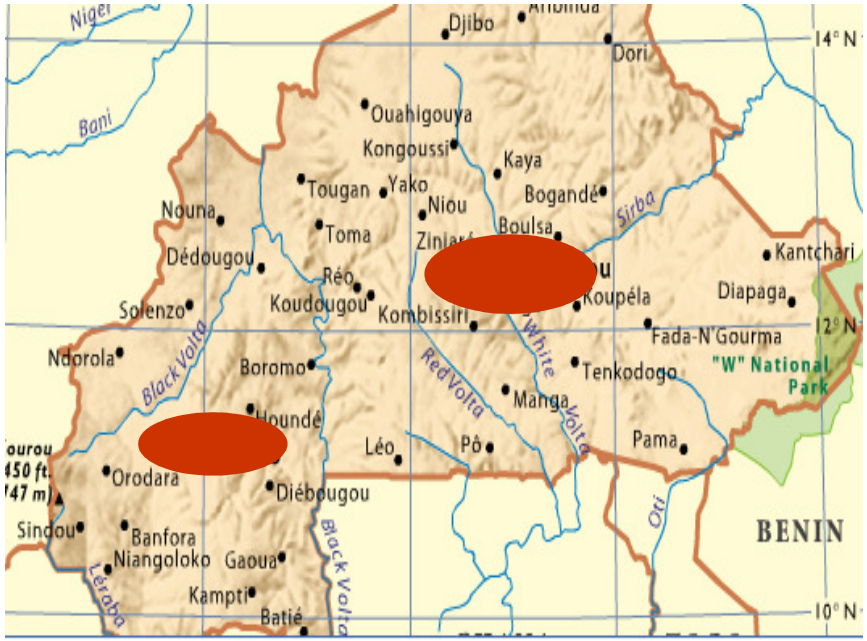
www.who.int/hiv/pub/drugresistance/report2012

TRANSMITTED HIV DRUG RESISTANCE in Low and Middle Income Countries

Transmitted HIVDR (WHO surveys) Overview of Methods

ARV-naïve populations likely to have been recently infected

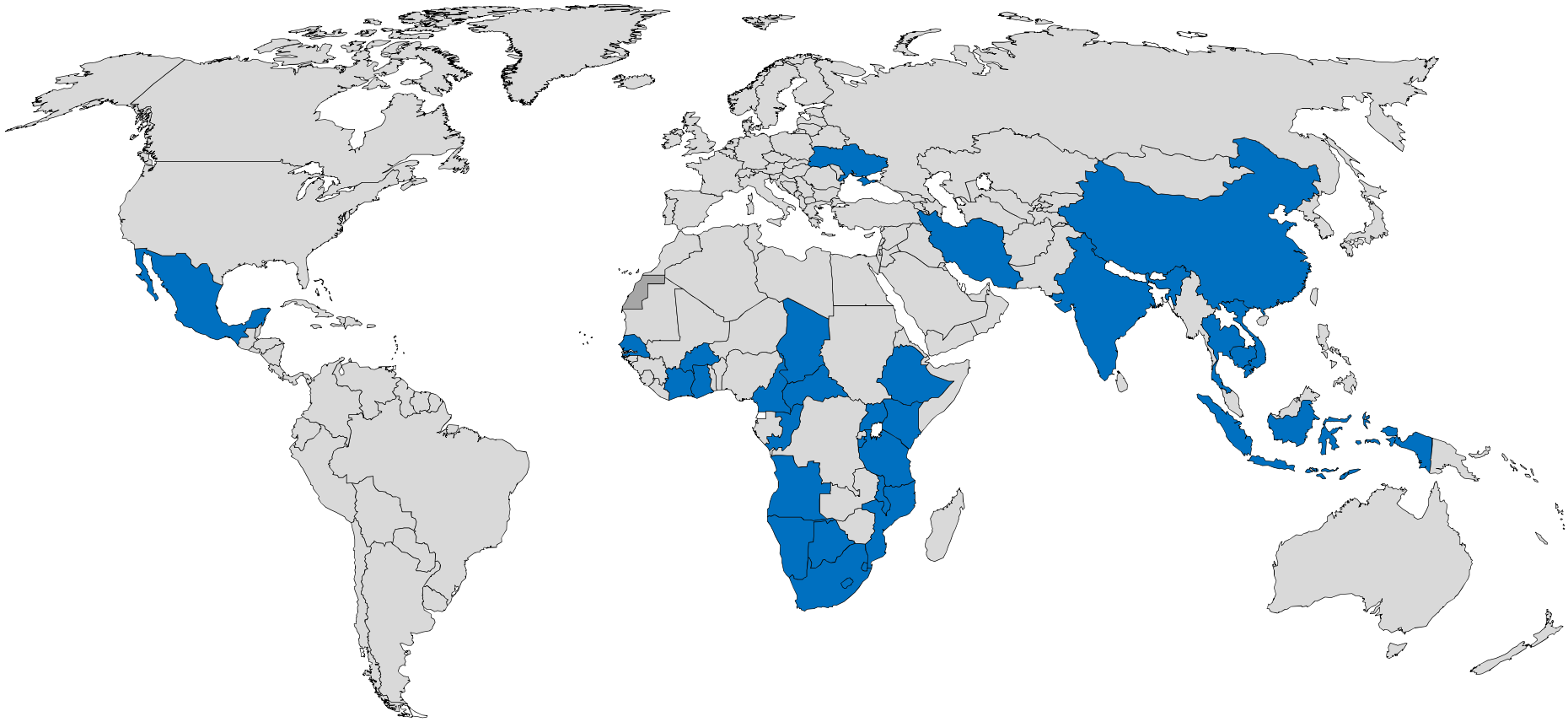
- **Results** not nationally representative but apply to the **geographic area surveyed within the country**



M.Myatt et al. Antiviral Therapy 2008
D.Bennett et al. Antiviral Therapy 2008

Transmitted HIVDR (WHO surveys) Geographical Distribution (pooled analysis)

82 surveys covering a total of 3588 recently-infected individuals, 2004-2010



Country reporting results from WHO surveys of transmitted HIV drug resistance, 2004–2010
No data available or not participating in the surveys
Not applicable

Transmitted HIVDR (WHO surveys)
Estimates by year and region (pooled analysis)

	2004	2005	2006	2007	2008	2009	2010	P-value*
ANY DRUG								
African Region	10.0 (2.8 to 23.7)	0.2 (0.0 to 1.4)	0.6 (0.0 to 2.4)	1.2 (0.1 to 3.2)	1.8 (0.1 to 4.8)	4.5 (2.3 to 7.2)	2.8 (0.1 to 7.7)	0.04
South-East Asia Region	…	0.7 (0.0 to 4.8)	2.2 (0.1 to 11.8)	1.0 (0.2 to 3.8)	…	…	…	-
Western Pacific Region	…	…	4.5 (1.0 to 9.6)	4.4 (1.1 to 9.4)	1.5 (0.0 to 4.3)	2.4 (0.6 to 4.8)	…	0.41
Americas	8.5 (2.4 to 20.4)	…	…	…	…	…	…	-
Europe Region	…	…	…	…	…	2.6 (0.1 to 6.9)	…	-
Eastern Mediterranean Region	…	…	7.7 (1.6 to 20.9)	…	…	…	…	-
Overall	**9.2** (3.7 to 16.4)	**0.3** (0.2 to 1.4)	**1.6** (0.4 to 3.2)	**1.6** (0.5 to 3.1)	**1.6** (0.3 to 3.5)	**3.4** (2.1 to 5.1)	**2.8** (0.1 to 7.7)	**0.06**

If you break down by drug class…

*Note: *test for trend, adjusted for region; Source: 82 WHO surveys covering 3588 recently-infected individuals*

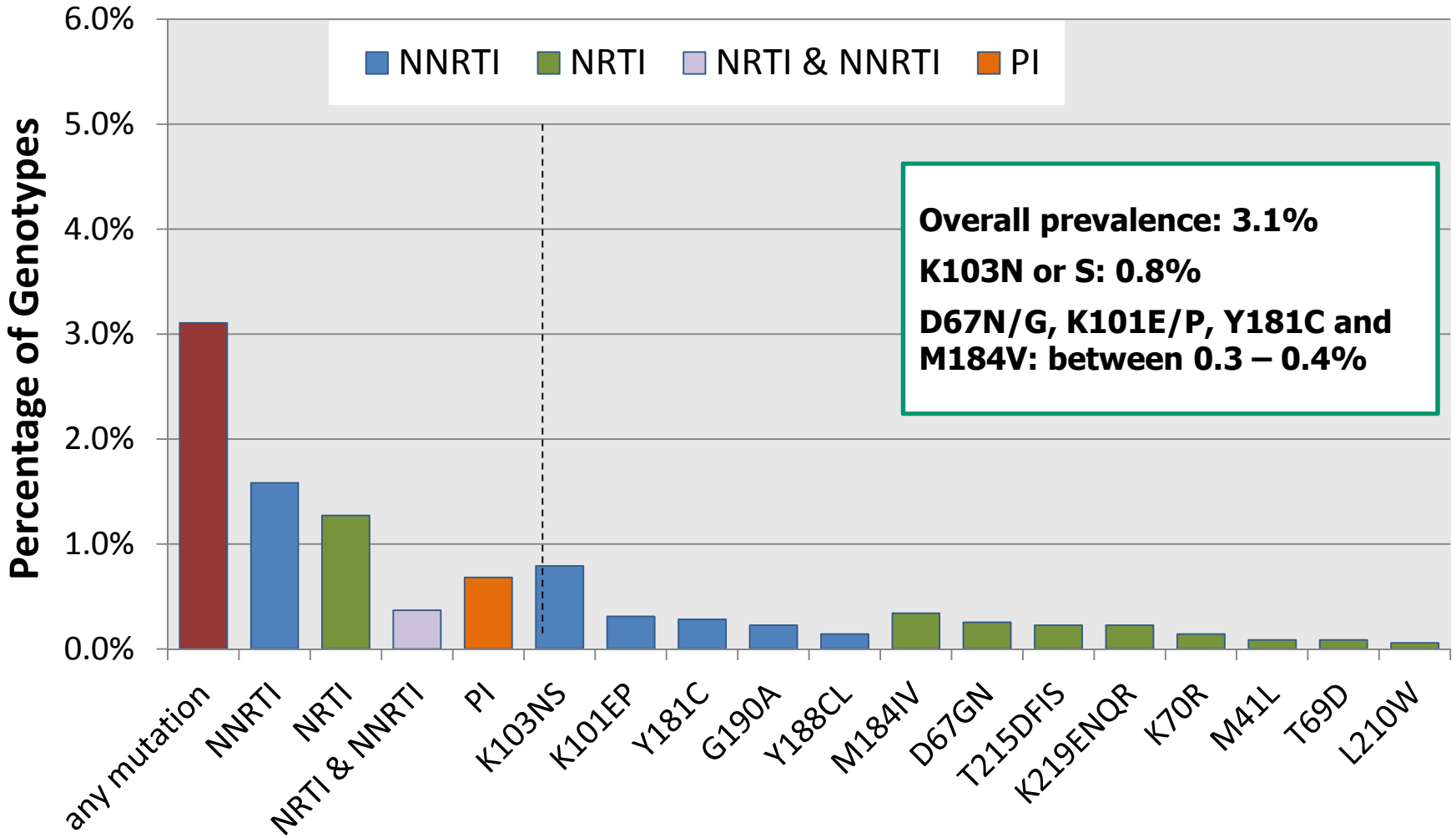
Transmitted HIVDR (WHO surveys) Estimates by year, region and class of drug

	2004	2005	2006	2007	2008	2009	2010	P-value*
NNRTI								
African Region	2.3 (0.1 to 12.0)	0.0 (0.0 to 1.0)	0.1 (0.0 to 0.9)	0.0 (0.0 to 0.7)	1.5 (0.1 to 3.9)	3.4 (1.8 to 5.2)	2.0 (0.2 to 5.0)	<0.01
Overall	0.7 (0.0 to 4.3)	0.0 (0.0 to 0.8)	0.2 (0.1 to 0.9)	0.3 (0.0 to 1.3)	0.9 (0.1 to 2.2)	2.0 (1.1 to 3.2)	2.0 (0.2 to 5.0)	<0.01
NRTI								
Overall	6.5 (2.0 to 12.8)	0.0 (0.0 to 0.8)	0.5 (0.0 to 1.4)	0.4 (0.0 to 1.4)	0.4 (0.0 to 1.4)	0.9 (0.3 to 1.7)	0.6 (0.0 to 3.7)	NS
PI								
Overall	0.7 (0.0 to 5.3)	0.1 (0.0 to 1.1)	0.2 (0.0 to 1.0)	0.3 (0.0 to 1.3)	0.0 (0.0 to 0.7)	0.5 (0.0 to 1.2)	0.0 (0.0 to 1.1)	NS

… estimated increase is only statistically significant for NNRTI in Africa.

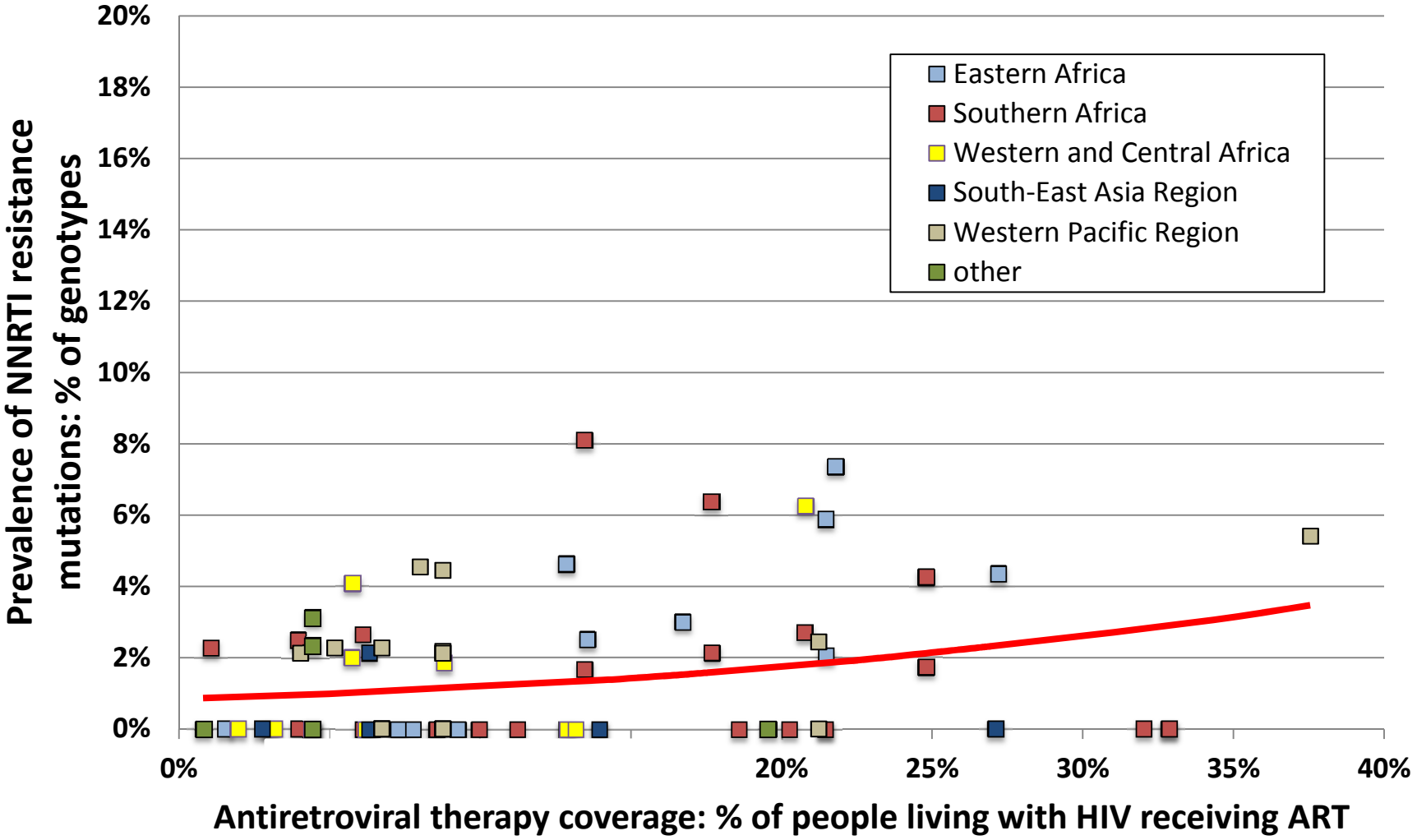
*Note: *test for trend, adjusted for region; Source: 82 WHO surveys covering 3588 recently-infected individuals; all other regions omitted due to lack of statistical significance. Areas surveyed variec considerably among countries and over time..*

Transmitted HIVDR (WHO surveys) Mutation Prevalence (n=3588, pooled analysis from 82 surveys)



Note: drug resistance mutations as defined by WHO 2009 Surveillance Drug Resistance Mutation (SDRM) list

Transmitted HIVDR (WHO surveys) Relationship between transmitted resistance to NNRTI and ART coverage



Notes: p-value adjusted for region: 0.039. Odds-ratio = 1.49 (95% CI 1.07-2.08)

ACQUIRED HIV DRUG RESISTANCE in Low and Middle Income Countries

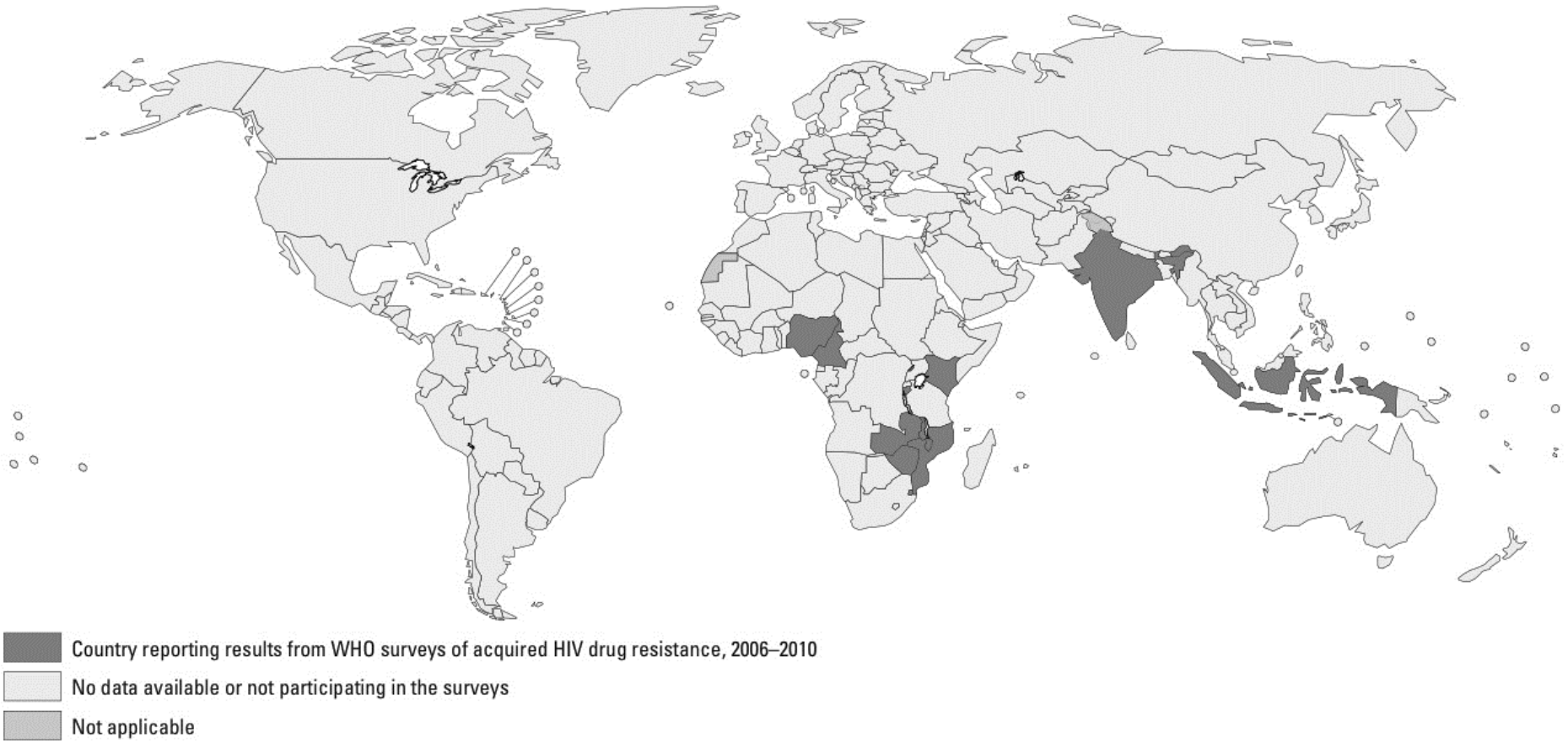
Acquired HIVDR – WHO surveys

Populations starting 1st-line ART at select clinics (naïve- and ARV-exposed)

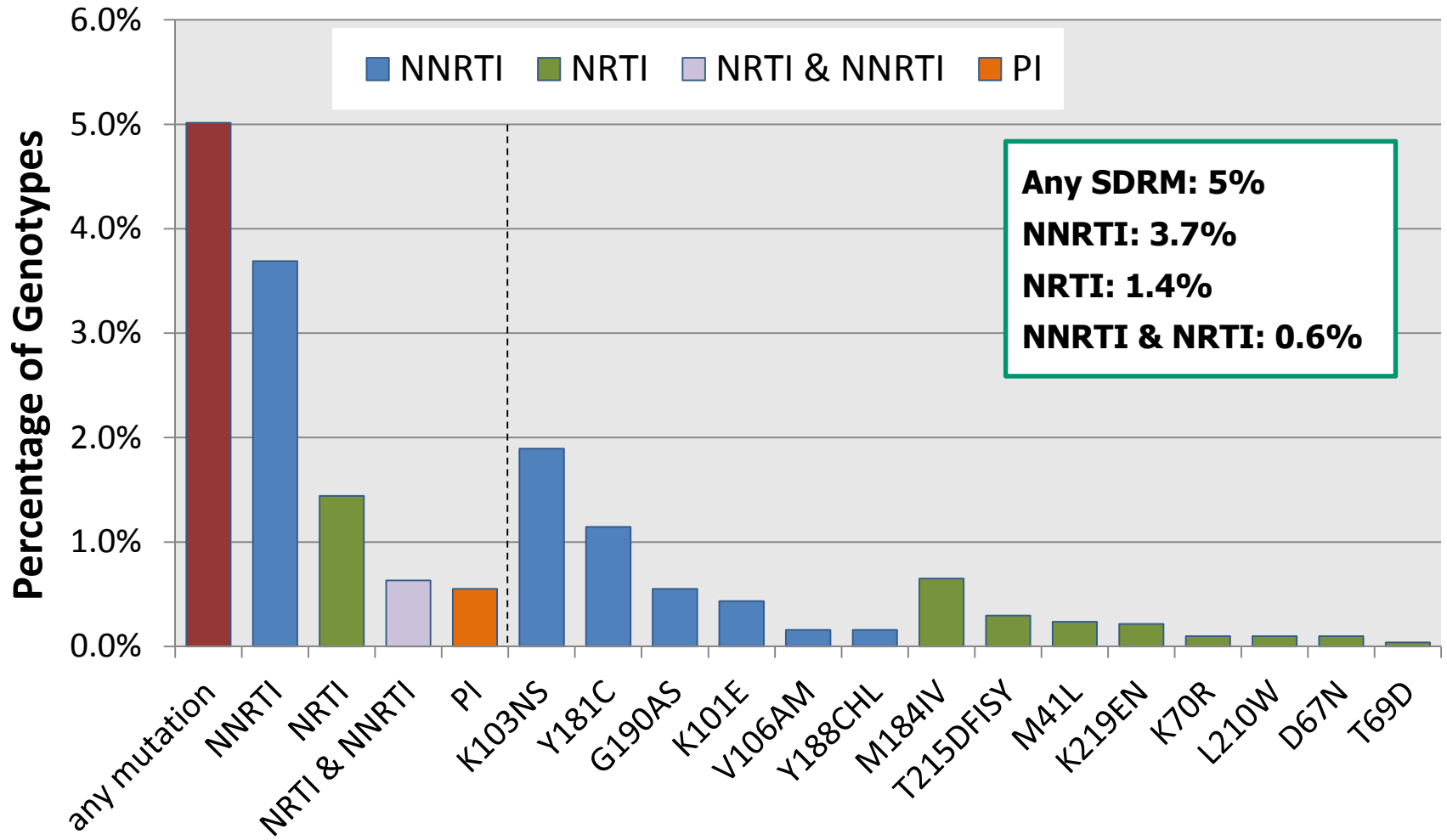
Objectives

- To describe HIVDR in cohorts prior ART initiation
- To estimate viral load suppression and resistance 12 months after ART initiation

Acquired HIVDR (WHO surveys)
40 surveys, 12 countries, 2006 – 2010



Acquired HIVDR (WHO surveys)
Mutation Prevalence at ART initiation (N = 5094)



Note: drug resistance mutations as defined by WHO 2009 Surveillance Drug Resistance Mutation (SDRM) list

Acquired HIVDR (WHO surveys)
HIVDR in Patients before ART Initiation (N = 5094)

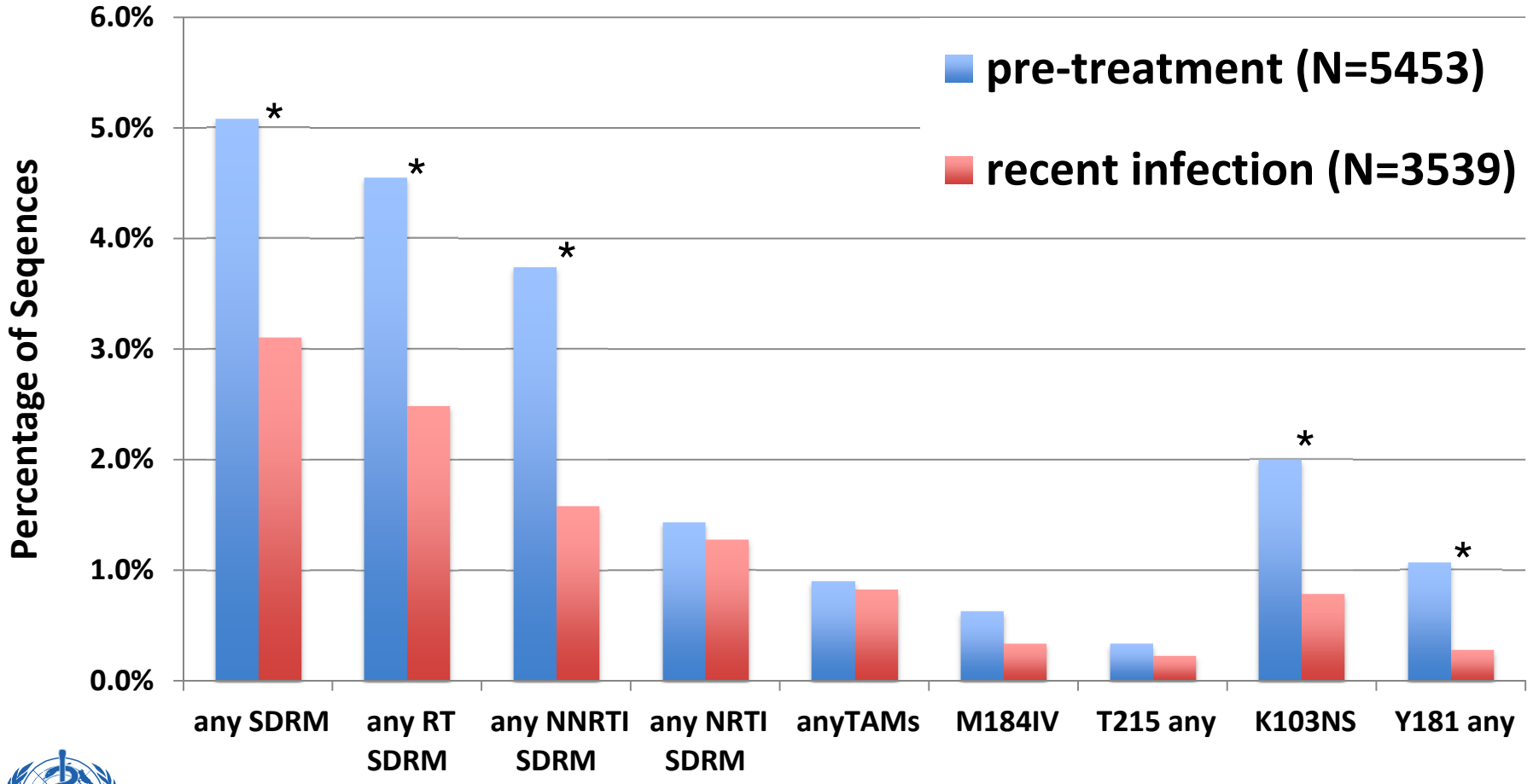
		Year of Implementation				
		2007	2008	2009	2010	*p-value*
Any drug class	Africa	4.6 (3.6–5.8)	3.7 (2.8–4.8)	4.6 (2.2–7.8)	6.8 (4.8–9.0)	0.04
	South-East Asia	7.9 (4.0–13.7)	5.4 (2.9–8.6)	…	…	0.34
	Overall	**4.8 (3.8–6.0)**	**3.9 (3.0–4.9)**	**4.6 (2.2–7.8)**	**6.8 (4.8–9.0)**	**0.06**

Acquired HIVDR (WHO surveys)
HIVDR in Patients Before ART Initiation (N = 5094)

		Year of Implementation				
		2007	2008	2009	2010	*p-value*
Any drug class	Africa	4.6 (3.6–5.8)	3.7 (2.8–4.8)	4.6 (2.2–7.8)	6.8 (4.8–9.0)	0.04
	South-East Asia	7.9 (4.0–13.7)	5.4 (2.9–8.6)	…	…	0.34
	Overall	4.8 (3.8–6.0)	3.9 (3.0–4.9)	4.6 (2.2–7.8)	6.8 (4.8–9.0)	0.06
NRTI	Africa	1.1 (0.6–1.7)	1.0 (0.5–1.6)	1.1 (0.3–2.2)	1.0 (0.3–2.0)	0.75
	South-East Asia	3.6 (1.2–8.2)	4.3 (2.0–7.2)	…	…	0.74
	Overall	1.2 (0.7–2.0)	1.3 (0.8–2.0)	1.1 (0.3–2.2)	1.0 (0.3–2.0)	0.70
NNRTI	**Africa**	**3.4 (2.4–4.5)**	**2.3 (1.4–3.3)**	**3.3 (1.8–5.0)**	**5.4 (3.7–7.4)**	**0.03**
	South-East Asia	7.9 (4.0–13.7)	3.0 (1.2–5.6)	…	…	…
	Overall	**3.7 (2.5–4.9)**	**2.4 (1.6–3.3)**	**3.3 (1.8–5.0)**	**5.4 (3.7–7.4)**	**0.06**
PI	Africa	0.3 (0.1–0.8)	0.5 (0.1–0.9)	0.5 (0.1–1.7)	0.0 (0.0–0.4)	0.82
	South-East Asia	0.0 (0.0–2.6)	0.0 (0.0–0.7)	…	…	…
	Overall	0.3 (0.0–0.7)	0.4 (0.1–0.8)	0.5 (0.1–1.7)	0.0 (0.0–0.4)	0.97

Note: "…" not available or applicable; select p-values could not be calculated due to collinearity, lack of data and/or variability

DR Mutation Prevalence in Recent Infection vs. Pre-treatment (WHO surveys)



*p<0.05 (Fisher Exact test with correction for multiple comparisons)

Acquired HIVDR (WHO surveys) Three 12-Month Outcomes (n=3834)

(1) HIV drug resistance prevented:

- VL <1000 copies/ml

(2) HIV drug resistance detected:

- VL > 1000 copies/ml and HIVDR

(3) HIV drug resistance possible:

- LTFU, stops and VL > 1000 copies/ml but no HIVDR observed

Acquired HIVDR (WHO Surveys)
Summary of 12-Month Outcomes (pooled, n=3834)

Region	Resistance prevention (% of people initiating ART[a])	Any resistance at endpoint[b]		Possible resistance (% of people initiating ART[a])
		% of people initiating ART[a]	% of people failing with genotype available	
Eastern Africa	79.4%	4.3%	63.7%	16.4%
Southern Africa	80.3%	4.7%	73.3%	15.0%
Western/central Africa	59.9%	6.0%	74.5%	34.1%
African Region	**76.6%**	**4.7%**	**69.5%**	**18.8%**
South-East Asia	**71.4%**	**8.9%**	**93.3%**	**19.7%**
Overall	**76.1%**	**5.1%**	**72.1%**	**18.8%**

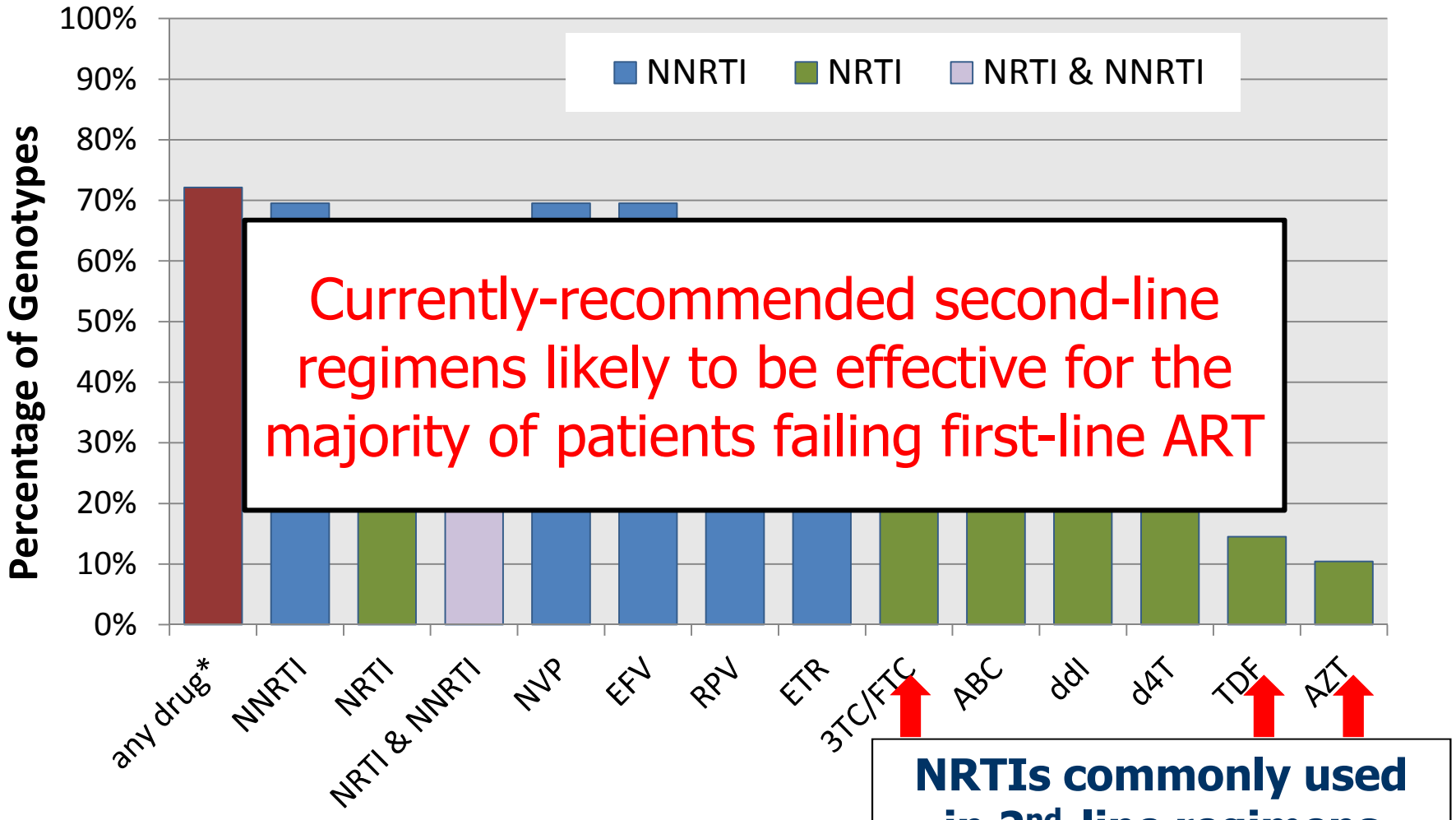
[a]Excludes people who died or who were transferred to another antiretroviral therapy facility. [b]HIV drug resistance defined as a drug resistance prediction of low, intermediate or high level using the Stanford HIV database algorithm. Alternatively, if calculated based on the number of surveillance drug resistance mutations at endpoint, subregional, regional and overall proportions remain identical.

Acquired HIVDR (WHO Surveys)
Summary of 12-Month Outcomes (pooled, n=3834)

Region	Resistance prevention (% of people initiating ART[a])	Any resistance at endpoint[b]		Possible resistance (% of people initiating ART[a])
		% of people initiating ART[a]	% of people failing with genotype available	
Eastern Africa	79.4%	4.3%	63.7%	16.4%
Southern Africa	80.3%	4.7%	73.3%	15.0%
Western/central Africa	59.9%	6.0%	74.5%	34.1%
African Region	**76.6%**	**4.7%**	**69.5%**	**18.8%**
South-East Asia	**71.4%**	**8.9%**	**93.3%**	**19.7%**
Overall	**76.1%**	**5.1%**	**72.1%**	**18.8%**

27.9% of patients failing therapy had wild type

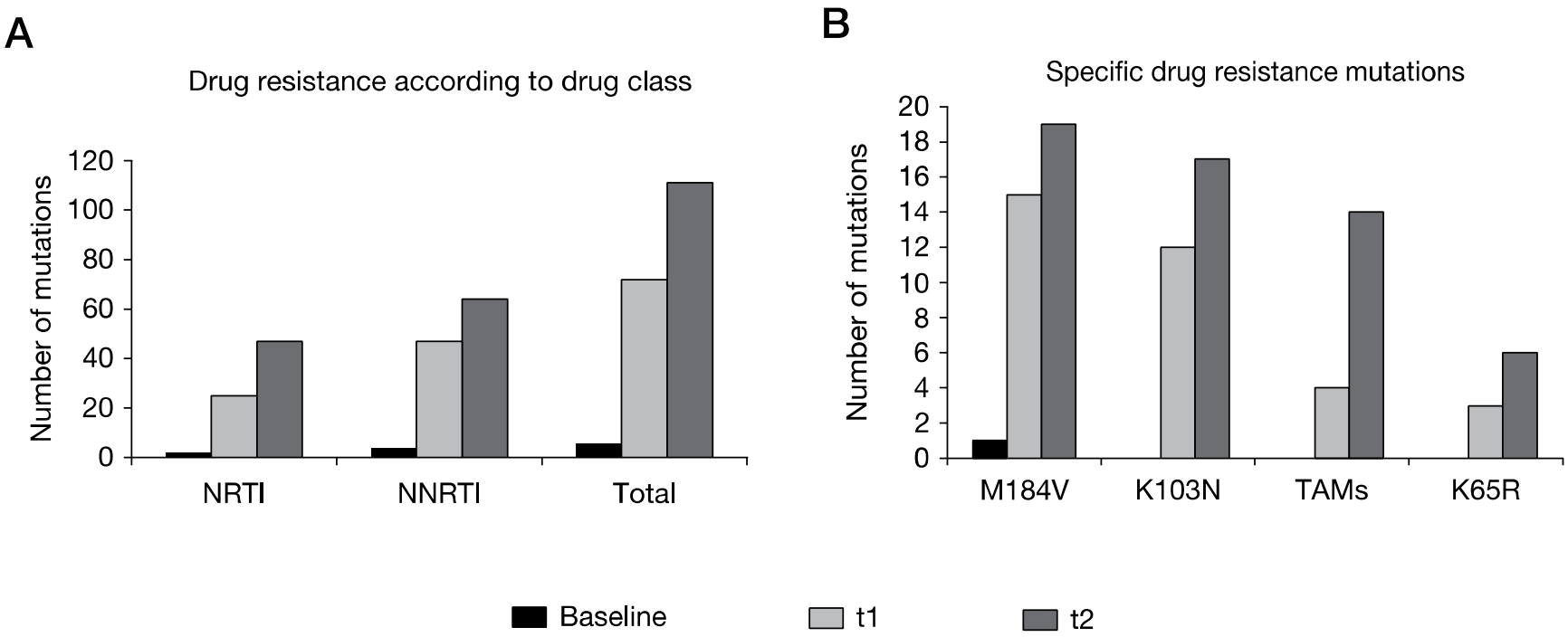
Acquired HIVDR (WHO Surveys)
Predicted HIVDR in people failing ART at 12 months (n=269)



* PI resistance was only observed for nelfinavir, resulting from the presence of multiple polymo
CRF02_AG. Nelfinavir resistance was never observed in specimens without predicted NRTI or NNRTI resistance. No drug resistance was predicted for any ritonavir-boosted PI. Based on the Stanford algorithm using resistance interpretation of "low-level" or higher.

Rapid accumulation of mutations when first-line ART is continued despite virological failure

Longitudinal genotyping analysis at first detection of Virological Failure (t1) and 6 or 12 months after (t2) *(Barth et al, AVT, 2012)*



Steep increase in TAMs (+250%) and K65R (+100%) between t1-t2

NNRTI susceptibility is already lost at first detection of VF

Second-Line Antiretroviral Treatment Successfully Resuppresses Drug-Resistant HIV-1 After First-Line Failure: Prospective Cohort in Sub-Saharan Africa

Kim C. E. Sigaloff,[1,2] Raph L. Hamers,[1,2] Carole L Wallis,[3] Cissy Kityo,[4] Margaret Siwale,[5] Prudence Ive,[3] Mariette E. Botes,[6] Kishor Mandaliya,[7] Maureen Wellington,[8] Akin Osibogun,[9] Wendy S. Stevens,[3] Michèle van Vugt,[10] and Tobias F. Rinke de Wit,[1,2] the PharmAccess African Studies to Evaluate Resistance (PASER)

- ✓ VF at 12 months: 14% (28/201)
- ✓ 53% of the participants were predicted to receive partially active second-line regimens

Table 2. Risk Factors for Second-Line Failure

	Virological Failure[a]			
Factor	Events (%)	Univariate	Multivariate	*P*
Activity of second-line regimen[c]				
Fully active	31 (29.8)	1.0	1.0	
Partially active	30 (23.4)	0.72 (0.38–1.36))	0.80 (0.33–1.91)	.610

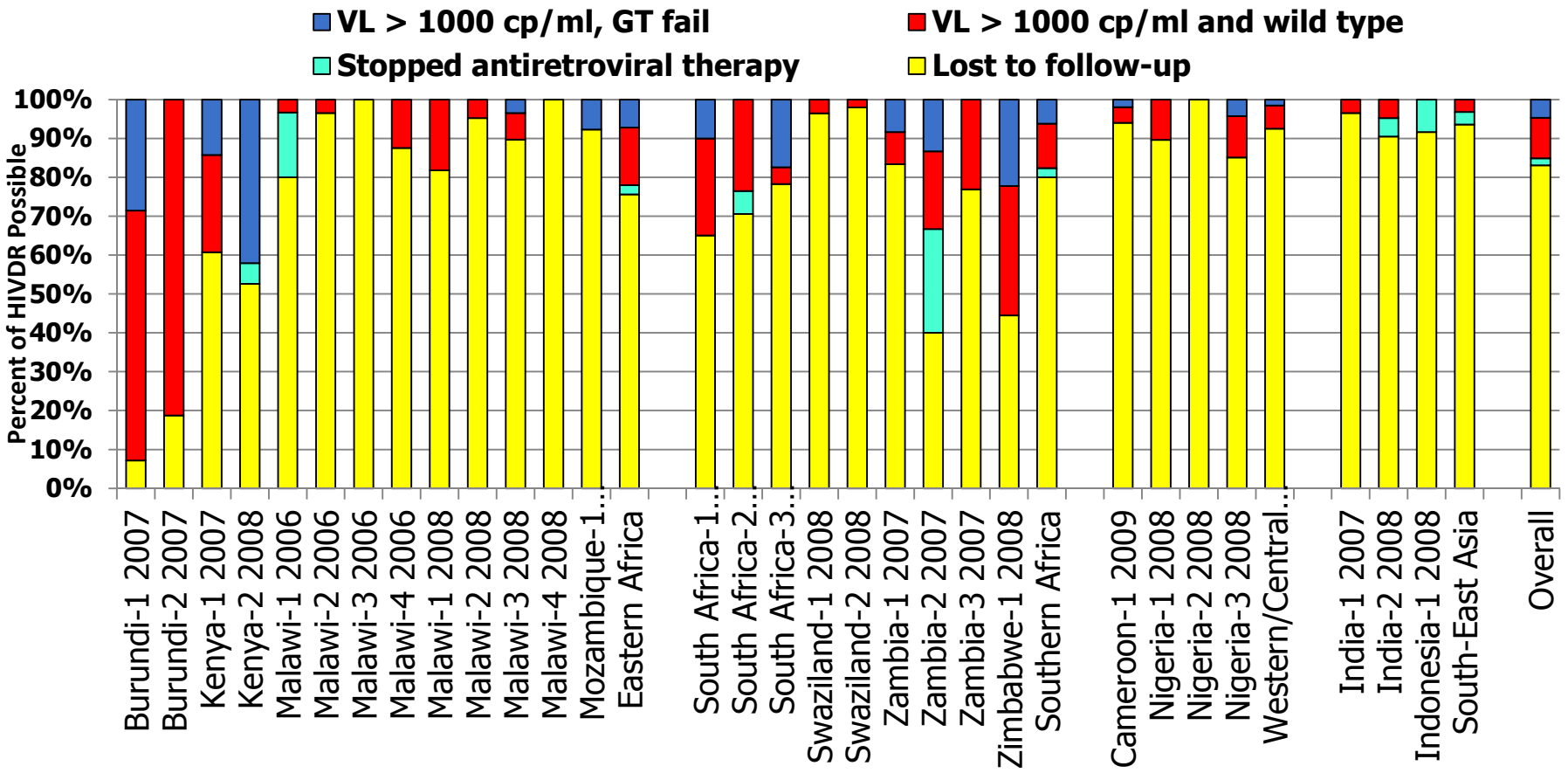
Empirically prescribed bPI-second line ART can successfully resuppress HIV after 1st line failure, even in the absence of a fully active NRTI backbone *Sigaloff, JID, 2012*

Acquired HIVDR (WHO Surveys)
Summary of 12-Month Outcomes (pooled, n=3834)

Region	Resistance prevention (% of people initiating ART[a])	Any resistance at endpoint[b]		Possible resistance (% of people initiating ART[a])
		% of people initiating ART[a]	% of people failing with genotype available	
Eastern Africa	79.4%	4.3%	63.7%	16.4%
Southern Africa	80.3%	4.7%	73.3%	15.0%
Western/central Africa	59.9%	6.0%	74.5%	34.1%
African Region	**76.6%**	**4.7%**	**69.5%**	**18.8%**
South-East Asia	**71.4%**	**8.9%**	**93.3%**	**19.7%**
Overall	**76.1%**	**5.1%**	**72.1%**	**18.8%**

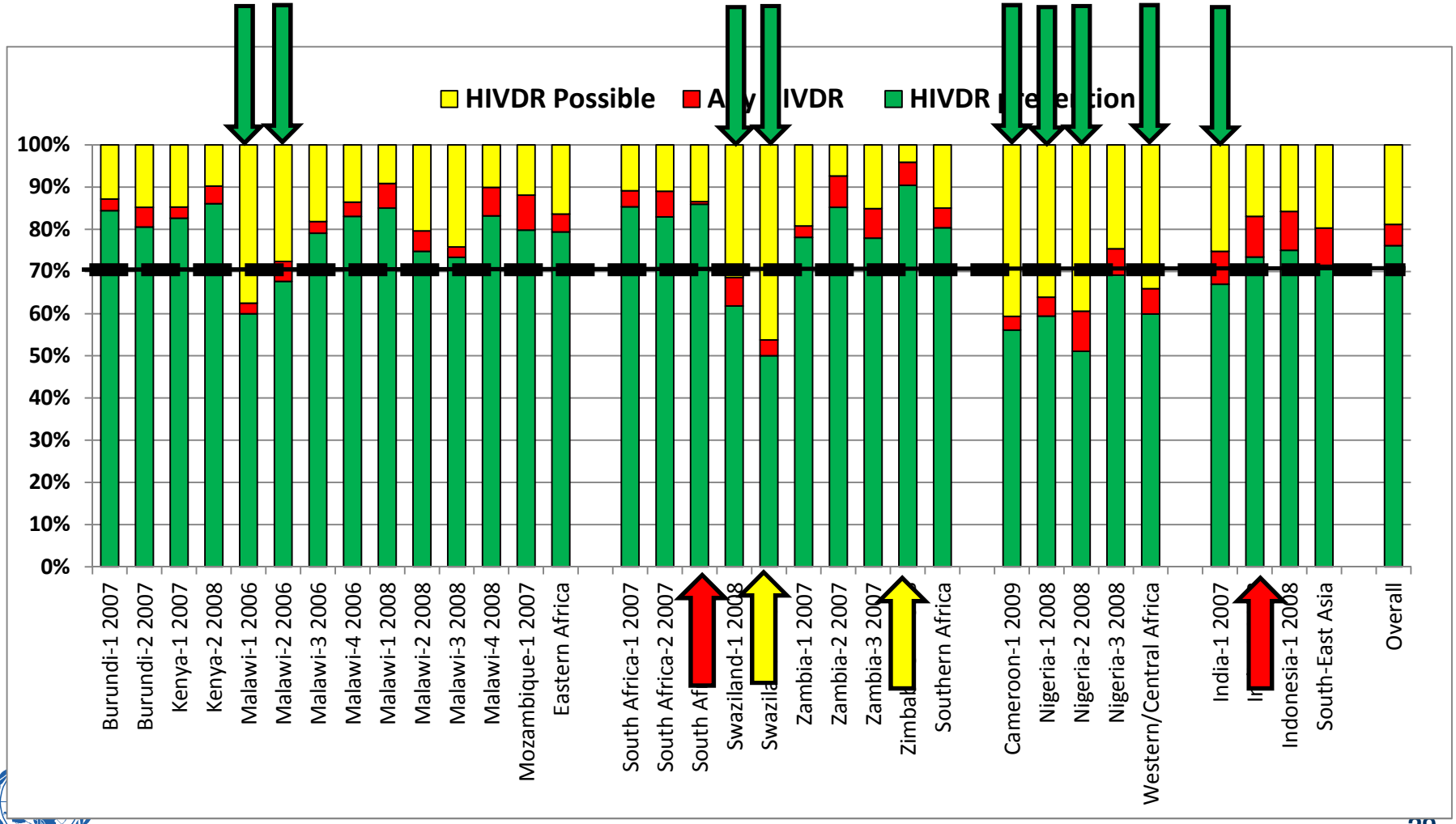
[a]Excludes people who died or who were transferred to another antiretroviral therapy facility. [b]HIV drug resistance defined as a drug resistance prediction of low, intermediate or high level using the Stanford HIV database algorithm. Alternatively, if calculated based on the number of surveillance drug resistance mutations at endpoint, subregional, regional and overall proportions remain identical.

Acquired HIVDR (WHO Surveys) – 12-month outcomes: HIVDR possible (by clinic)



Possible drug resistance driven primarily by losses to follow-up

Acquired HIVDR (WHO Surveys) – Summary of key 12-month outcomes (by clinic)



Note: Possible drug resistance includes 75 patients with viral load greater than 1000 copies/ml at 12 months and no resistance, 13 who stopped antiretroviral therapy, 599 who were lost to follow-up, 34 with viral load greater than 1000 copies/ml at 12 months but with specimens failing to amplify and 1 with viral load greater than 1000 copies/ml at switch but failing to amplify PCR products

Conclusions (I)

- ✓ **Transmitted resistance** (particularly to NNRTI) in recently infected people **increasing** over time in areas surveyed in Africa, **but still within the expected levels (3.4%** in 2009**)**
- ✓ In 2010, HIVDR in **pre-treatment** population:
  5.4% (3.7-7.4) to **NNRTI;** 6.8% (4.8-9.0) overall
- ✓ **Currently recommended first-line ART regimens still effective for most people initiating treatment**

Conclusions (II)

- Response to first-line ART is excellent at 12 month (90% OT, 76% ITT)
- Attention to:
  I. **unnecessary switch** for ~30% people failing ART with wild type
  II. **"possible" DR** (particularly LTFU) ~18% of people initiating ART
- At 12 month, DR patterns largely preserve NRTIs for 2nd line
- 2nd-line ART still effective (12 month endpoint) despite partially active NRTI-backbone

ACKNOWLEDGEMENTS

Bill and Melinda Gates Foundation

Members of HIVResNet in particular Neil Parkin, Diane Bennett Karen Kelley, Annemarie Wensing, Elliot Raizes, Scott Hammer, Mark Wainberg, Andrew Phillips, Andrea De Luca, Anna Hearps, Mark Wainberg, Scott Hammer, and Wataru Sugiura; Mark Myatt and Don Sutherland; Anne-Mieke Vandamme, Jonathan Schapiro, Rami Kantor and Robert Shafer;
Tommy Liu, Robert Shafer, Alexandra Calmy
VQA/NIH Program
ANRS
Tufts University School of Medicine
Tulio de Oliveira, Tobias F. Rinke de Wit, Raph Hamers and Kim Sigaloff from (PASER), and the United States Centers for Disease Control and Prevention (CDC).

Countries who contributed with their data: Angola, Botswana, Burkina Faso, Burundi
Cameroon, Chad, Cote d'Ivoire, Ethiopia
India, Indonesia, Malawi, Mexico, Mozambique
Namibia, Nigeria, Senegal, South Africa, Swaziland
Tanzania, Thailand, Uganda, Viet Nam, Zimbabwe

WHO HIVDR Laboratory Network: Chunfu Yang, Martine Peeters, Paul Sandstrom, Christiane Adje, Almaz Abebe, Avelin Aghokeng, Clement Zeh, Coumba Toure Kane and Souleymane Mboup, Mariza Morgado, Luke Hanna, Srikanth Tripathy and Ramesh Paranjape, Siriphan Saeng-aroon, Ruengpung Sutthent, Shao Yiming, Ping Zhong, Hong Shang, Gillian Hunt, Johanna Ledwaba, and Lynn Morris, Chris Parry and Pontiano Kaleebu, Georges Dos Santos, Anna Hearps, Vicki Edouard, Adele Lee-Wriede and Suzanne Crowe, Wendy Stevens, Yasuhiro Yamamura, Leon McNally, Philip Cunningham, James Brooks, Patricia Pinson, Herve Fleury, Rob Schurman, Carmen Mendoza, Vincente Soriano, Pat Cane

Staff from WHO offices: including Emil Asamoah-Odei, Richard Banda, Fatim Cham, Christopher Dye, Guy-Michel Gershy-Damet, Noreen Jack, Patrick Kombate-Noudjo, Paul Assimawe Pana, Brian Pazvakavambwa, Giovanni Ravasi, Nirina Razakasoa, Padmini Srikantiah, Dongbao Yu