HIVDR in Infants

Protocol for Surveillance of HIVDR

among ART naive children

< 18 months of age newly diagnosed with HIV

Survey Design

Retrospective cross-sectional survey of DR-HIV prevalence among children diagnosed with HIV by Early Infant Diagnosis (EID) [PCR] methodology using remnant DBS specimens.

Data were abstracted from laboratory requisition forms that accompany DBS samples

- No identifying information were collected; the analysis was unlinked and anonymous.
- Results will not be returned (genotyping will be performed six months to a year after children should already have started ART)

Inclusion Criteria

- DBS collected from a **child < 18 months of age who received testing for EID**.
- The DBS specimen tested HIV-positive by DNA PCR.
- At **least one viable remnant DBS** was available if not required for clinical testing or quality assurance (Two-four DBS would be optimal)
- DBS specimen has been **no more than 30 days at room temperature**, then stored at -20°C or -80°C with no thawing before genotyping will be performed.

Exclusion Criteria

Child is receiving three or more ARV drugs for the purpose of treatment of HIV at time of blood draw.

Required Variables

- Date of birth; if not available, age of child in months at time of blood draw
- Gender
- Site name where DBS was collected
- Site type where DBS was collected
- Date of DBS collection
- Date of first freezing DBS at -20 C or -70 C
- Date of PCR assay

Highly desirable variables

- Is child breastfeeding at time of specimen collection?
- ARVs received by mother for PMTCT or maternal health(Yes/No)
- ARVs received by child for PMTCT (Yes/No)
- ARVs received by mother sd-NVP; sd-NVP + ZDV; ZDV + 3TC; a three-ARV regimen (for maternal health or prophylaxis)
- ARVs received by child for PMTCT: sd-NVP; extended NVP; 6 weeks of ZDV; 6 weeks of NVP + ZDV

Statistical Analysis

- Univariate logistic regression model
- Multivariate logistic regression model
- PMTCT and Neonatal prophylaxis levels were investigated in the multivariate model.
- Interaction between PMTCT and neonatal prophylaxis was also explored

Contributing sites

- PMTCT, Maternal and Child Health (MCH) or Antenatal (ANC) clinics providing HIV-testing as part of routine follow-up of children < 18 months of age.

- Hospitals or other medical facilities providing HIV testing to symptomatic children < 18 months of age.

- Provider initiated testing and counseling (PITC) sites or Voluntary Counseling and Testing (VCT) sites providing HIV testing for children < 18 months of age.

Participating laboratories

- Ideally, each lab **in the country** performing child EID will participate and will contribute to the overall sampling (feasible in countries with a limited number of diagnostic laboratories).

Case Definition

Drug-resistant HIV

(Standard sequencing to detect quasi-species present at 20% or higher. *Only the RT region of the HIV genome will be sequenced***)**

-Any mutation or combination of mutations that produce low, intermediate, or high level resistance to a relevant ARV drug or drug class according to the latest Stanford HIVDR database scores

-A Stanford classification of "potential" drug resistance will not classified as drug resistance for the purpose of this survey.

Fasta files representing sequences will be imported into the database, so mutations at all positions will be available for analysis

Sample Size calculations based on:

- "true DR-HIV prevalence" of 50%
- 95% confidence intervals (CI) +/- 7%
- Power = 0.80
- non-amplification rate of 20%
- *These "conservative" assumptions yield the largest sample size and the most precise estimates of prevalence with the most narrow confidence intervals*

Sample Size Examples

In Zimbabwe there is one EID laboratory:

In countries where only one laboratory participates, **the sample size will be 245**.

In Uganda there are eight EID laboratories:

We use a design effect of 2 if more than one laboratory participates. The final effective sample size if more than one laboratory participates is 245 x 2 = 490

Pilot Phase


Kariba
Lake Kariba
Chinhoyi
Harare
Livingstone
Victoria Falls
Kadoma
ZIMBABWE
Mutare
Gweru
Sabi
Bulawayo
Lundi

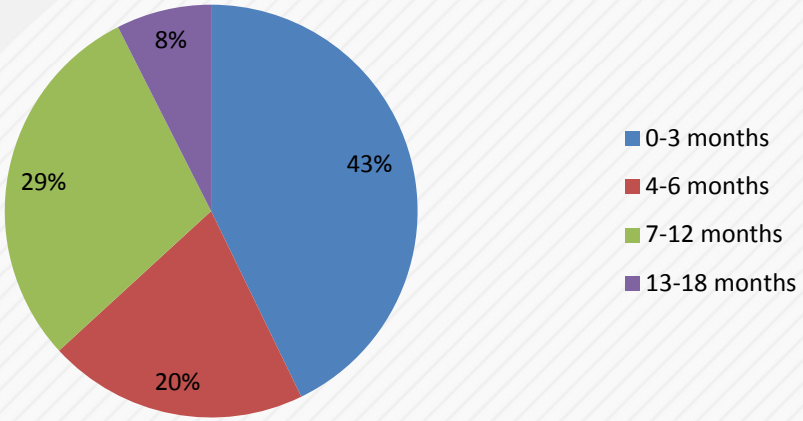

Mozambique
South Africa
Piggs Peak
Maputo
Mbabane (Administrative)
Lobamba
Manzini
Siteki
Swaziland
Hlatikulu


MALAWI
Ruvuma
Lake Nyasa
Pemba
Cape Delgado
COMOROS
Mayotte
ZAMBIA
Nampula
Moçambique
Cabora Bassa Dam
MOZAMBIQUE
Tete
Zambezi
Quelimane
ZIMBABWE
Mozambique Channel
Beira
Save
Limpopo
Inhambane
Indian Ocean
SOUTH AFRICA
SWAZILAND
MAPUTO

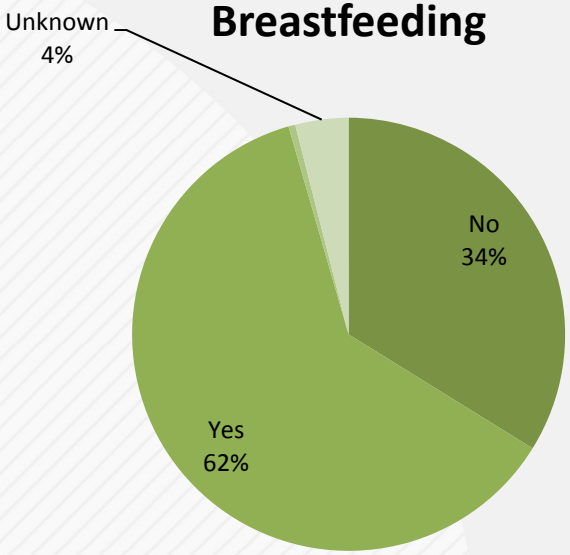
Swaziland

(201 DBS specimens)

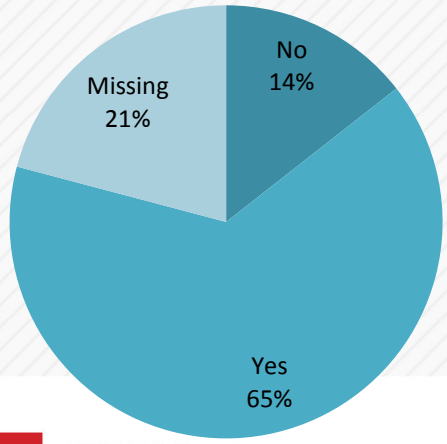
Age groups



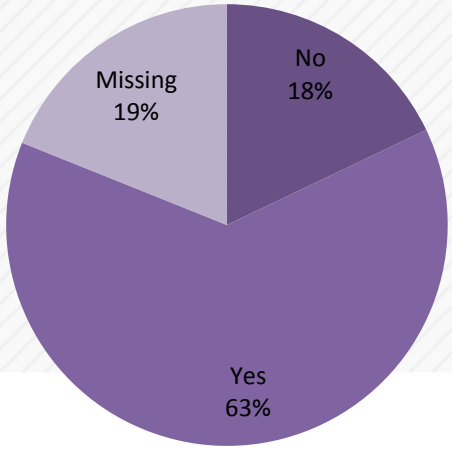
Breastfeeding



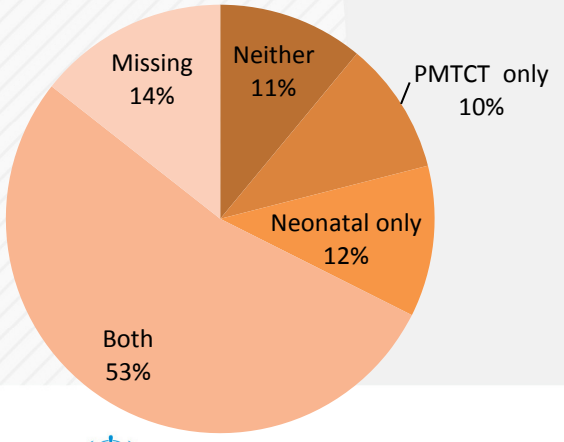
Neonatal prophilaxis



PMTCT



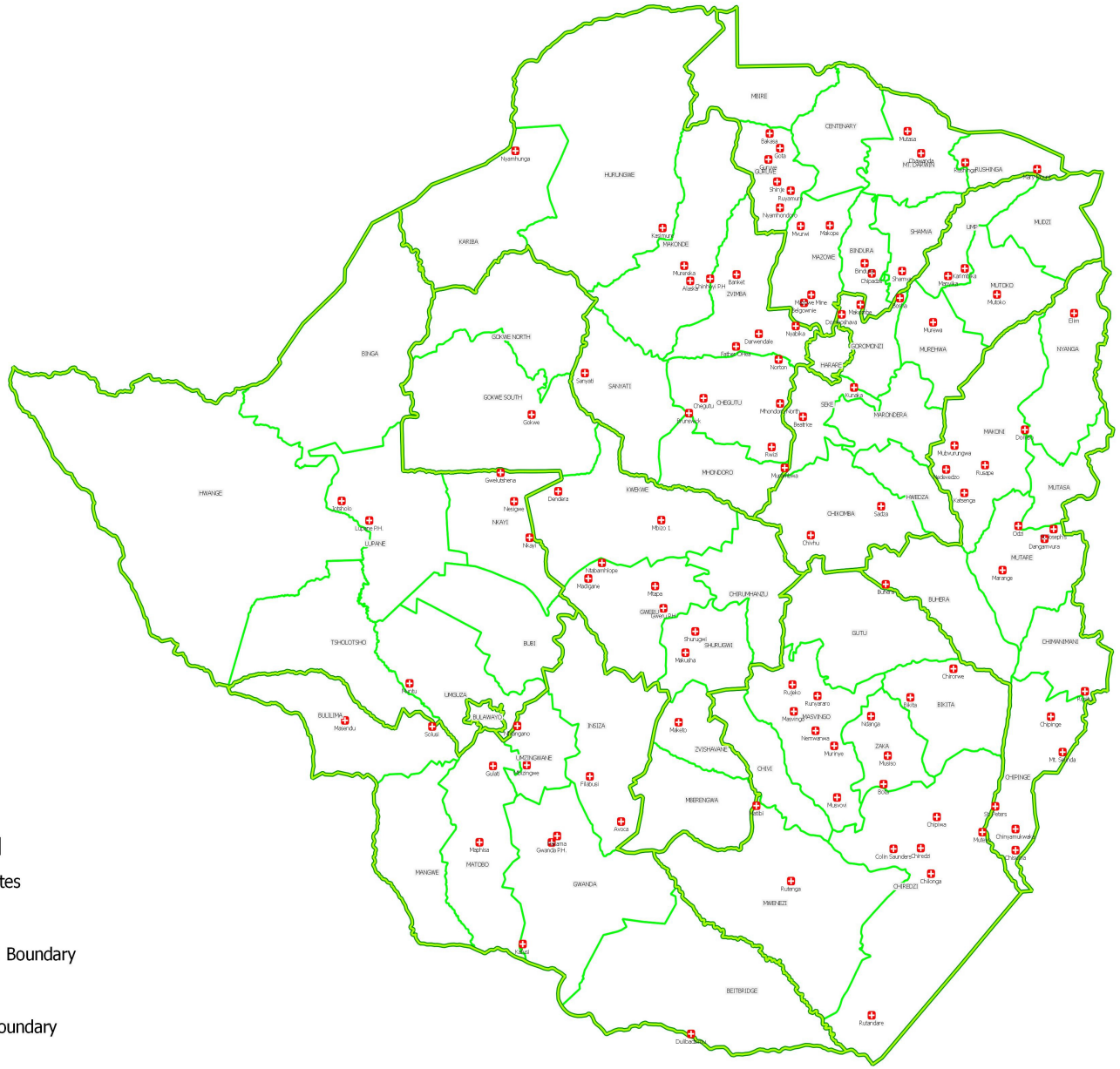
PMTCT & Neonatal prophylaxis



HIV/AIDS Department

World Health Organization

Paediatric HIV Drug Resistance Survey Sites



Legend

Survey Sites

Provincial Boundary

District Boundary

Harare Survey Sites

Braeside Clinic
Budiriro Polyclinic
Cranborne Clinic
Epworth Clinic
Glenview Polyclinic
Harare Hospital
Kambuzuma Polyclinic
Mabelreign Clinic
Mabvuku Polyclinic
Marlborough Satelite
Mufakose Polyclinic
Overspill Clinic
Parirenyatwa Hospital

Chitungwiza Hospital
Seke North Clinic
Seke South Clinic
South Medical Hospital
St Mary's Clinic
Zengeza Polyclinic

Bulawayo Sites

Emakhandeni Clinic
Magwegwe Clinic
Mpilo Hospital
Mzilikazi Clinic
Njube Clinic
Pelandaba Clinic
Tshabalala Clinic

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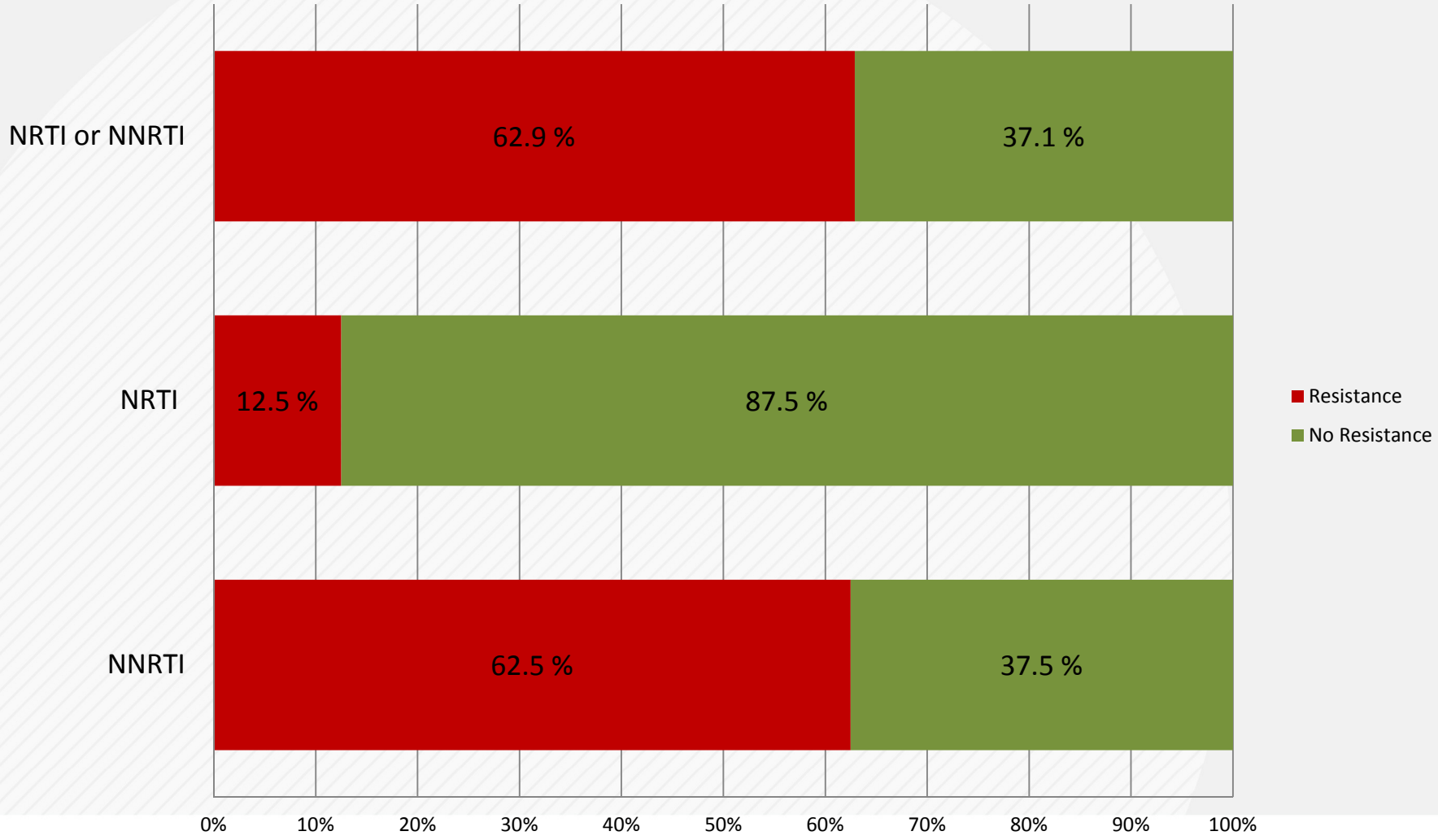
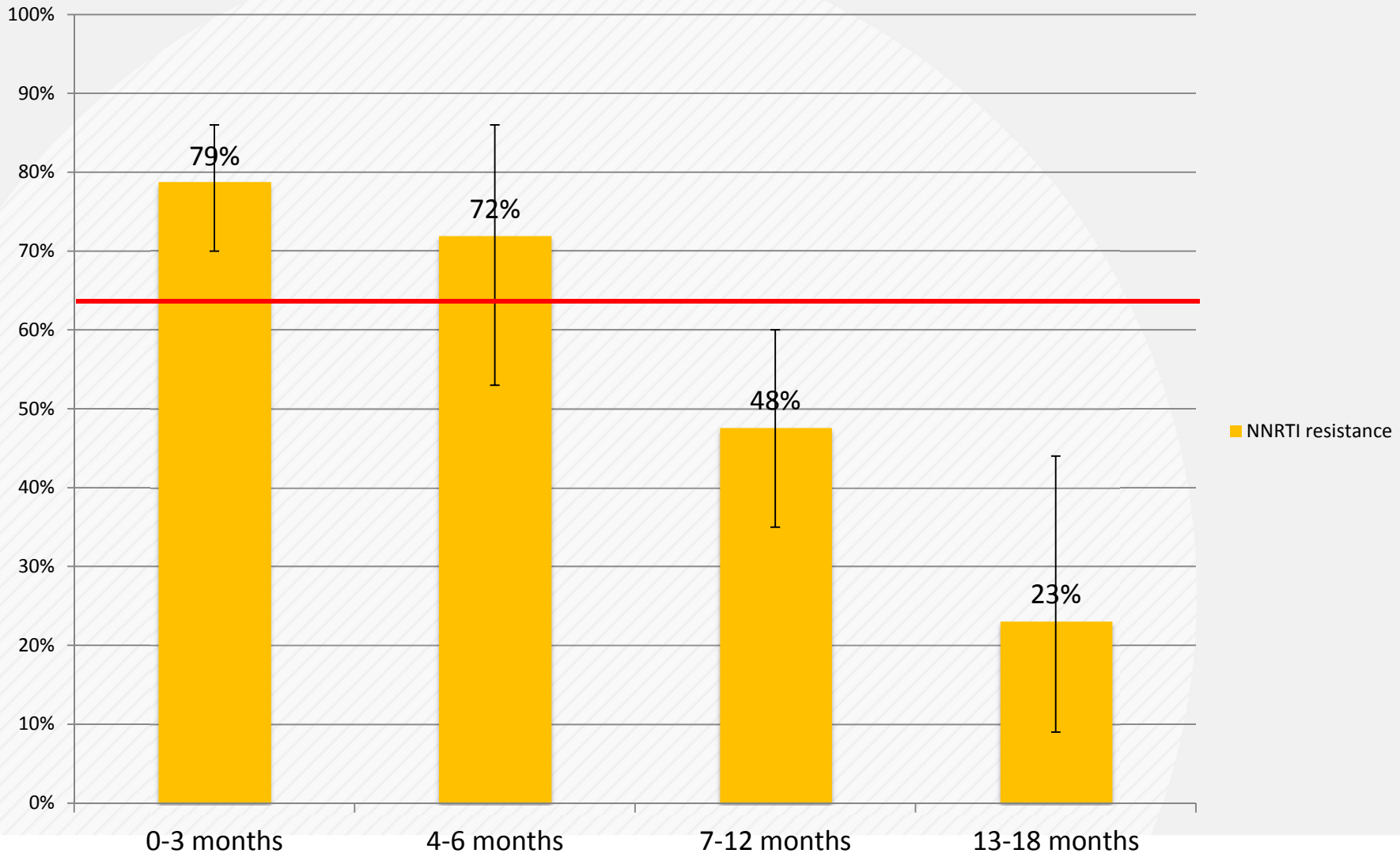
Ministry of Health and Child Welfare
in Collaboration with the
World Health Organisation

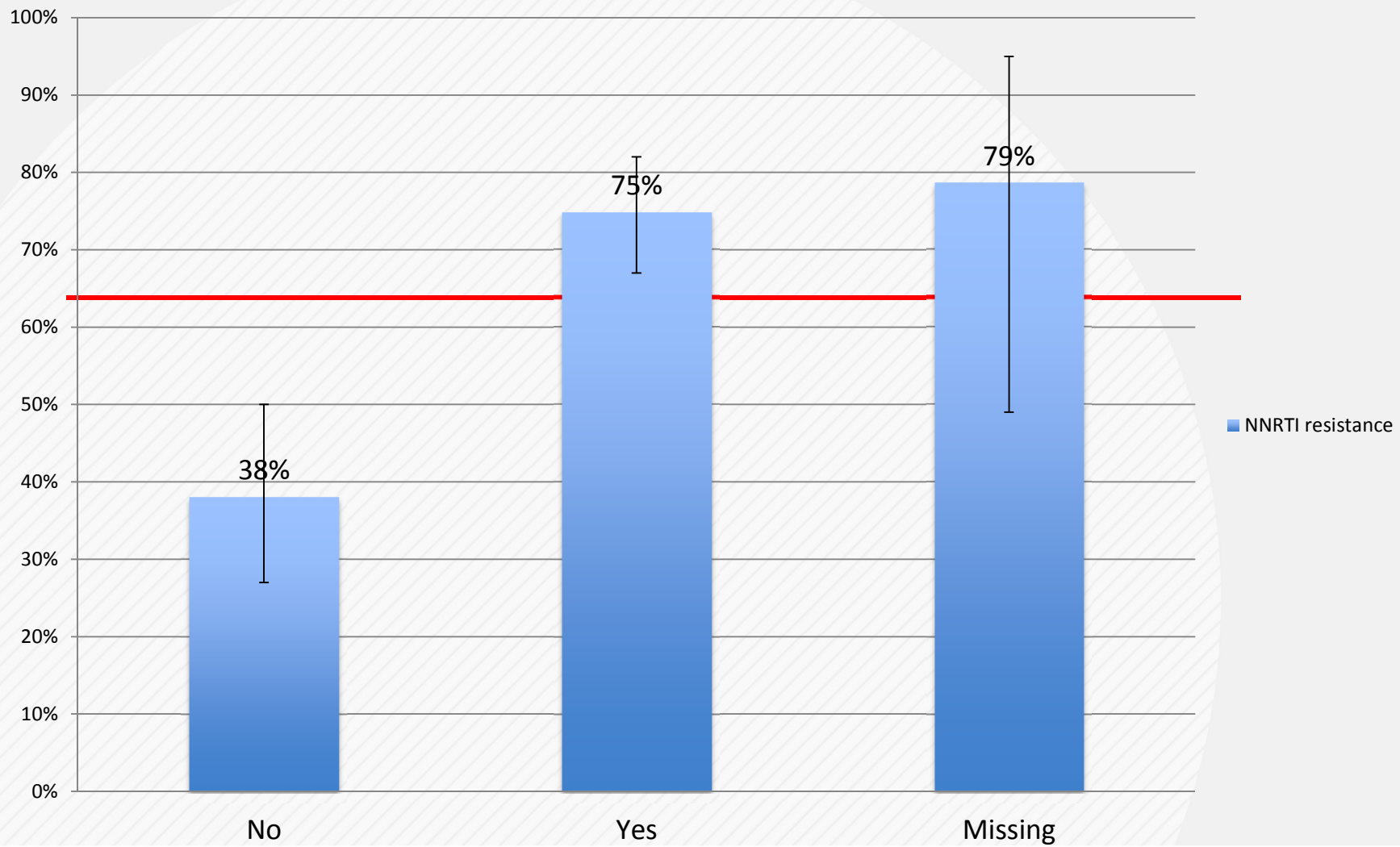
Resistance


NRTI or NNRTI
62.9 %
37.1 %
NRTI
12.5 %
87.5 %
NNRTI
62.5 %
37.5 %
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Resistance
No Resistance

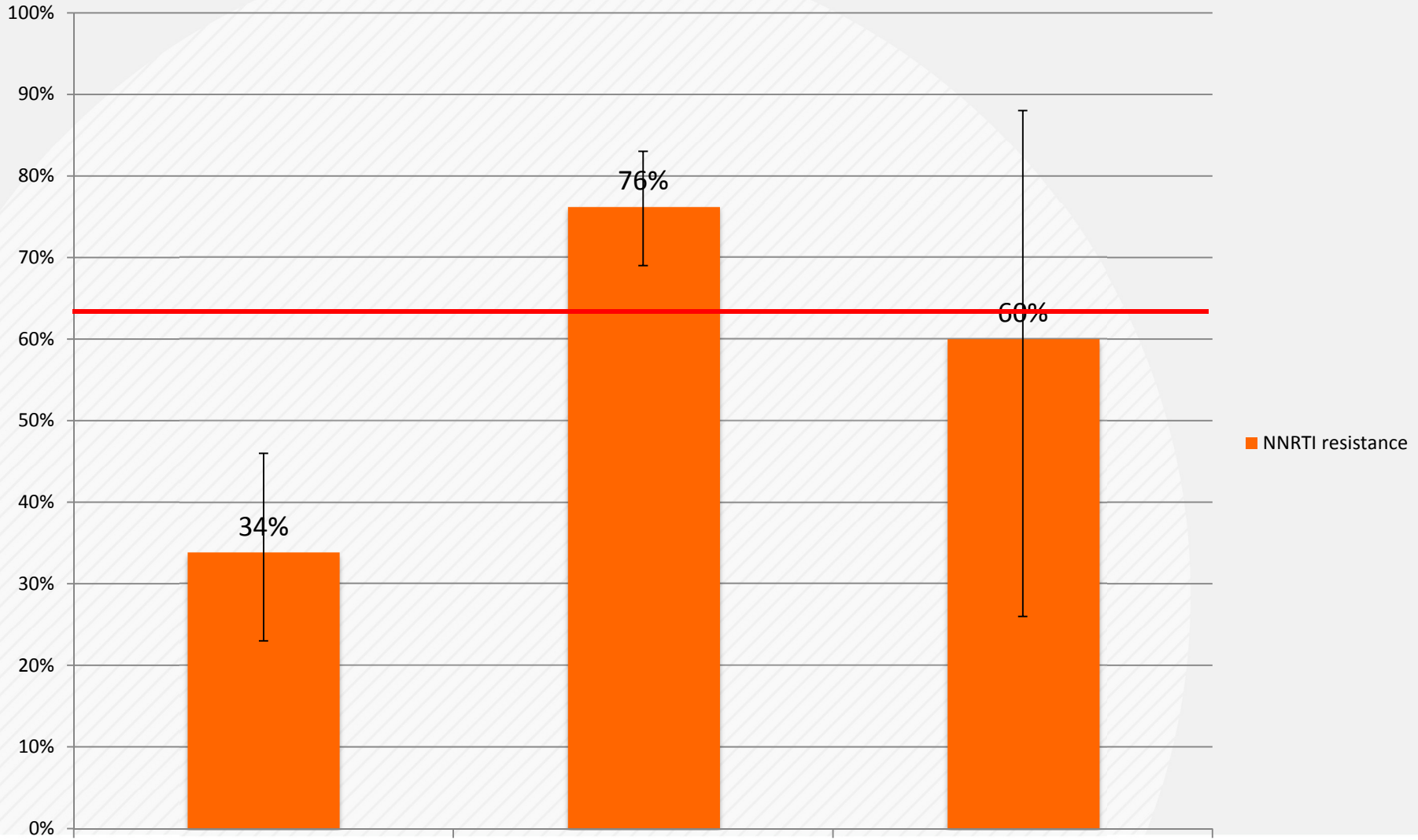
NNRTI resistance by age



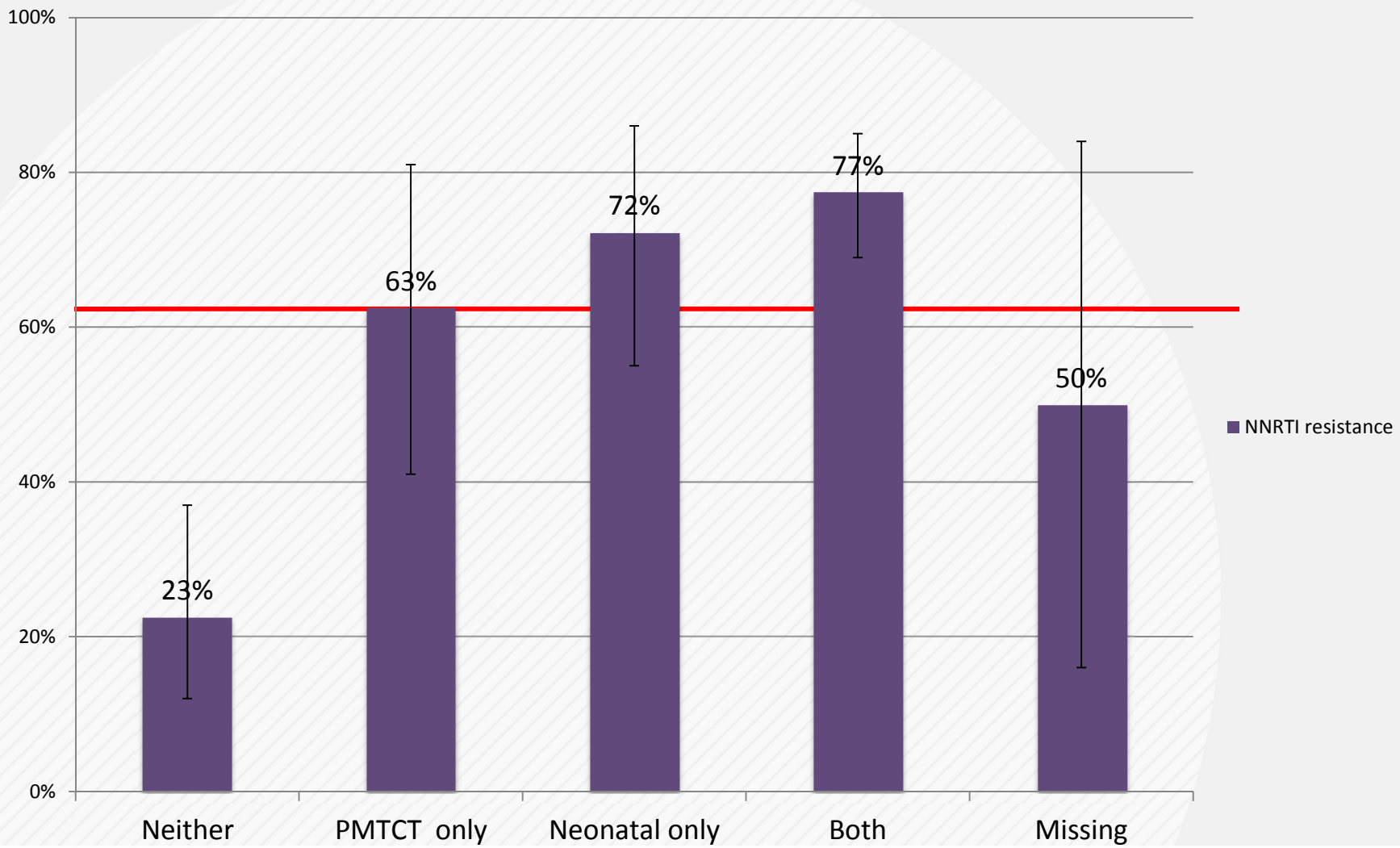
NNRTI resistance by PMTCT



NNRTI resistance by Neonatal Prophylaxis (NP)



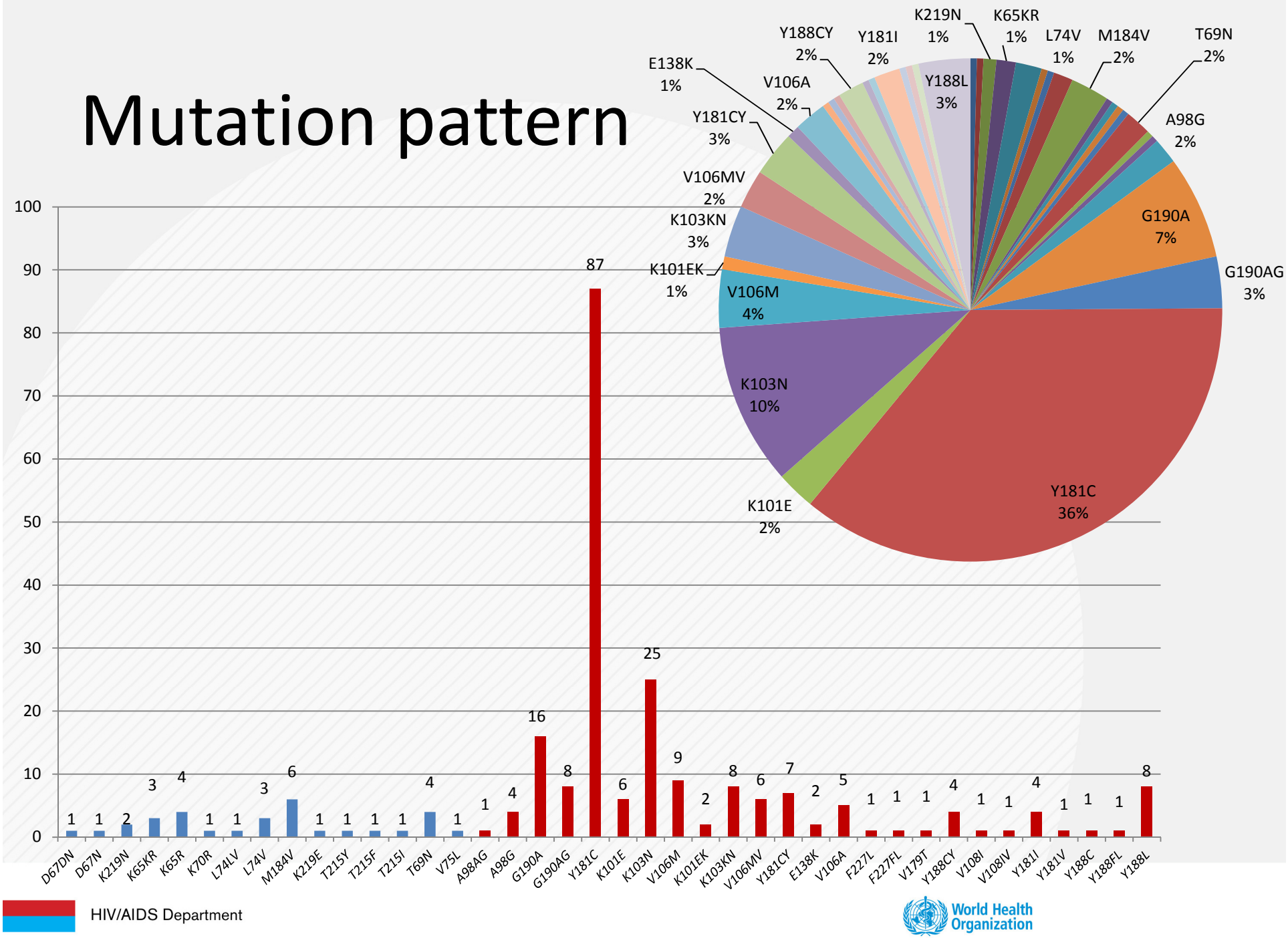
NNRTI resistance by PMTCT & NP



PMTCT/NP Regimens

Characteristic	Level	Total	%	NRTI	%	95%CI		NNRTI	%	95%CI		Either	%	95%CI	
Total		232	100	29	12.5	Lower	Upper	145	62.5	Lower	Upper	146	62.9	Lower	Upper
PMTCT regime	None or missing	93	40.1	6	6.5	0.02	0.14	41	44.1	0.34	0.55	42	45.2	0.35	0.56
	sdNVP only	15	6.5	0	0	-	-	11	73.3	0.45	0.92	11	73.3	0.45	0.92
	AZT from week 14 or 28	84	**36.2**	8	9.5	0.04	0.18	62	73.8	0.63	0.83	62	73.8	0.63	0.83
	ARV for mothers health	40	17.2	15	37.5	0.23	0.54	31	77.5	0.62	0.89	31	77.5	0.62	0.89
Neonatal prophylaxis	None or missing	81	34.9	7	8.6	0.04	0.17	30	37.0	0.27	0.49	31	38.3	0.28	0.50
	sdNVP only	2	0.9	0	-	-	-	0	-	-	-	0	-	-	-
	Extended NVP	115	49.6	14	12.2	0.07	0.20	92	80.0	0.72	0.87	92	80.0	0.72	0.87
	SdNVP + AZT 7 days	11	4.7	2	18.2	0.02	0.52	4	36.4	0.11	0.69	4	36.4	0.11	0.69
	NVP for 6 weeks	23	9.9	6	26.1	0.10	0.48	19	82.6	0.61	0.95	19	82.6	0.61	0.95

Mutation pattern

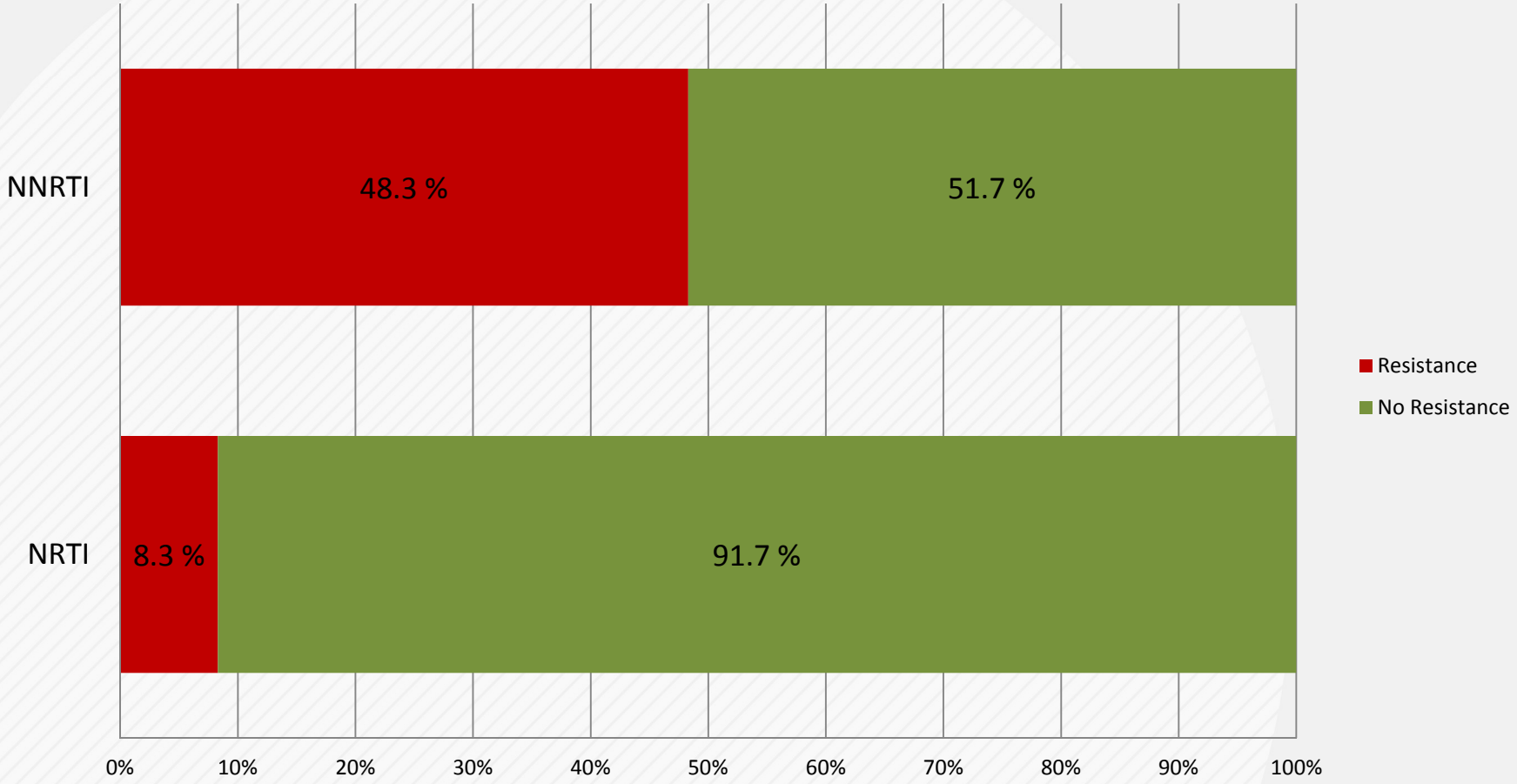


Predictors of NNRTI resistance

Characteristic	Adjusted Odds Ratio	Std. Err.	Wald Test (Z)	P-value	95% Conf. Interval Lower	Upper	LR X^2(P-value)
Age group							
0-3 months	1						
4-6 months	0.98	0.51	-0.05	0.96	0.35	2.72	
7-12 months	0.31	0.13	-2.91	< 0.01	0.14	0.68	
13-18 months	0.11	0.64	-3.80	< 0.01	0.04	0.35	
PMTCT group							
No	1						
Yes	3.12	1.19	2.98	< 0.01	1.48	6.58	
Neonatal prophylaxis group							
No	1						
Yes	2.78	1.10	2.60	0.01	1.29	6.02	62.20(< 0.01)
PMTCT regime*							
None	1						
sdNVP only	5.03	3.39	2.40	0.02	1.34	18.87	
AZT from week 14 or 28	4.12	1.53	3.82	< 0.01	1.99	8.53	
ARV for mothers health	5.97	2.89	3.68	< 0.01	2.31	15.43	57.66(< 0.01)
Neonatal prophylaxis#							
None	1						
sdNVP only	-	-	-	-	-	-	
Extended NVP	5.59	2.03	4.75	< 0.01	2.75	11.37	
sdNVP + AZT 7 days	1.73	1.26	0.75	0.45	0.42	7.19	
NVP for 6 weeks	6.83	4.29	3.06	< 0.01	1.99	23.41	60.87(< 0.01)

*Model adjusted for age and neonatal prophylaxis; # Model adjusted for age and PMTCT.

HIVDR prevalence: Combined analysis
(433 DBS specimens)



Predictors of HIVDR: Combined analysis

Characteristic	Adjusted Odds Ratio	Std. Err.	Wald Test (Z)	P-value	95% Conf. Interval Lower	Upper	LR X^2(P-value)
Country							
Swaziland	1						
Zimbabwe	6.35	1.87	6.27	< 0.01	3.56	11.30	
Age group							
0-3 months	1						
4-6 months	0.57	0.21	-1.53	0.13	0.28	1.17	
7-12 months	0.34	0.11	-3.34	< 0.01	0.18	0.64	
13-18 months	0.11	0.06	-4.28	< 0.01	0.04	0.31	
Breast feeding							
No	1						
Yes	0.72	0.24	-1.00	0.32	0.38	1.37	
Unknown/Mixed	1.82	1.96	0.56	0.58	0.22	15.07	
PMTCT							
No	1						
Yes	2.65	0.89	2.88	< 0.01	1.37	5.13	
Neonatal prophylaxis							
No	1						
Yes	3.53	1.28	3.48	< 0.01	1.74	7.18	105.72(< 0.01)
PMTCT regime*							
None	1						
sdNVP only	3.22	1.69	2.24	0.03	1.16	8.98	
sdNVP + tail AZT/3TC	-	-	-	-	-	-	
AZT from week 14 or 28	3.65	1.34	3.53	< 0.01	1.78	7.47	
AZT plus sdNVP + tail AZT/3TC	3.94	1.80	3.01	< 0.01	1.61	9.64	
ARV for mothers health	7.07	3.12	4.43	< 0.01	2.98	16.80	97.17(< 0.01)
Neonatal prophylaxis#							
None	1						
sdNVP only	-	-	-	-	-	-	
Extended NVP	7.24	2.34	6.13	< 0.01	3.85	13.64	
SdNVP + AZT 7 days	2.79	1.16	2.47	0.01	1.24	6.31	
NVP for 6 weeks	10.58	7.28	3.43	< 0.01	2.75	40.73	
AZT for 6 weeks	0.99	0.84	-0.02	0.99	0.19	5.22	120.83(< 0.01)

*Model adjusted for country, age, breastfeeding and neonatal prophylaxis; # Model adjusted for country, age, breastfeeding and PMTCT.

Conclusions

- **Irrespective of PMTCT exposure** NNRTI resistance in children less than 18 months can be as high as 63%.
- NNRTI resistance prevalence in children reported to be PMTCT **unexposed** can be as high as **38%.**
- NNRTI resistance prevalence in **"unknown" exposure** to PMTCT ranges **from 26% to 79%.**
- NNRTI resistance decrease remarkably over time