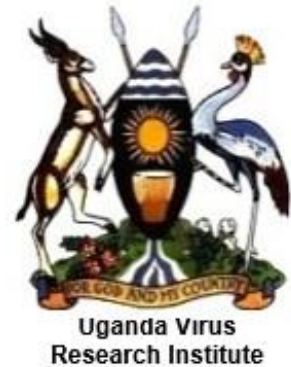




Uganda Virus Research Institute



HIV drug resistance and policy implications

Global Network of Antimicrobial Resistance and Infection
Prevention Symposium 4th March 2019

KAMPALA

Prof Pontiano Kaleebu

MRC/UVRI and LSHTM Uganda Research Unit

Outline

- ART access
- WHO strategy for HIVDR
- National Plan for HIVDR
- Findings, recommendations and implementation
- Global Action Plan for HIVDR
- Way forward
- Acknowledgements

ART Access

- Increased access to treatment-test and treat
- Goal: 90-90-90; 95-95-95
- By June 2018
 - 1,324,685 people were living with HIV
 - 1,189,811 (90%) knew their HIV status
 - 1,140,420 (96%) were on treatment
 - 992,165 (87%) had viral suppression



HIVDR can threaten achieving last "90"

Acquired HIVDR (ADR)



RESISTANCE

TREATMENT FAILURE



Pre-Treatment HIVDR (PDR)

WHO HIVDR prevention strategy

- Emergence of ARV drug resistance is inevitable, in view of the high replication and mutation rates of HIV and ART being lifelong.
- However, emergence of HIVDR can be delayed if ART services adhere to standard guidelines
- 2005 WHO recommended that countries develop a public-health strategy for prevention & monitoring of HIVDR
- The goal of the HIV Prevention Strategy:
“To minimize preventable emergence of HIV drug resistance, and to restrict the extent to which resistance jeopardizes the effectiveness of the limited ART regimens available, within the context of the national HIV prevention and treatment programmes”



The Republic of Uganda

**NATIONAL HIV DRUG RESISTANCE PREVENTION,
MONITORING AND SURVEILLANCE PLAN**

FY 2006/07-2010/11

Elements of National HIV Drug Resistance Prevention and Assessment Strategy

1. Establishment of a national HIVDR TWG and 5 year plan
2. Regular assessment of HIVDR "early warning" indicators (EWI) from all or representative ART sites
3. *Monitoring emerging HIVDR and associated factors in sentinel ART sites*
 - Pre-treatment HIVDR
 - Acquired HIVDR those on 1st line ART
 - Initial HIVDR among recently diagnosed infants identified at EID
4. Tracking HIVDR transmission in geographic areas where ART has been widespread for > 3 years
5. Development of a national HIVDR database
6. Establishment of an in-country WHO-certified HIVDR genotyping laboratory
7. Implementation of HIVDR prevention activities
8. Annual HIVDR report with appropriate recommendations

Stakeholder meetings

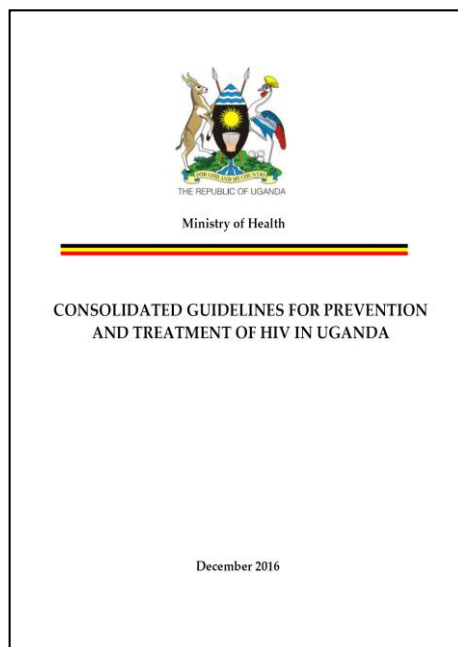
RECOMMENDATIONS FROM THE HIV DRUG RESISTANCE

STAKEHOLDERS MEETING

12th MARCH 2015, KAMPALA

Introduction

A stake holders meeting was held on the 12th of March 2015 at Imperial Royale Hotel, Kampala to get an update on the HIV drug resistance surveillance activities in the country. This was part of a two day's workshop organized by the Uganda Virus Research Institute (UVRI) on the 11th and 12th of March 2015. The theme of the workshop was "Working together for better HIV Laboratory Services and Improved delivery of prevention and care". The workshop consisted of a series of brief



Joint Clinical Research Centre

Vision: A Vibrant Self Sustaining Centre of Excellent in Medical Research, Training and Healthcare Services

Plot P93 Ring Road, Butikiro House- Mengo
P.O. Box 10005, Kampala Uganda
Fax: 256-414- 342632
Email: jrcr@jrcr.co.ug
Website: <http://www.jrcr.co.ug>



Telephone: 256-414-270283
270622
273515
342521
Helpline: 256-414-273062

OFFICE OF THE DIRECTOR

Dr. Christine Ondo

The Minister of Health
P.O. Box 8, Kampala

25th February 2013

Dear Madam;

Re: HIV Drug Resistance (HIVDR) Dissemination and Policy Meeting Report

We hereby present to you the summary report of the HIV Drug resistance research dissemination and policy meeting held 19th – 20th April 2012 at the Speke Resort Munyoyo. During this meeting some of the research work that the HIVDR committee and partner organizations are involved in was discussed and this provided a stage for technical exchanges and discussions

Organisers and Sponsors



ARTA
AIDS RESEARCH TRAINING AND
TECHNOLOGY AGENCY

aighd

NWO
National Organisation for Women's Research



Yours Sincerely;

Prof. Peter Mugenyi
Executive Director – JCRC

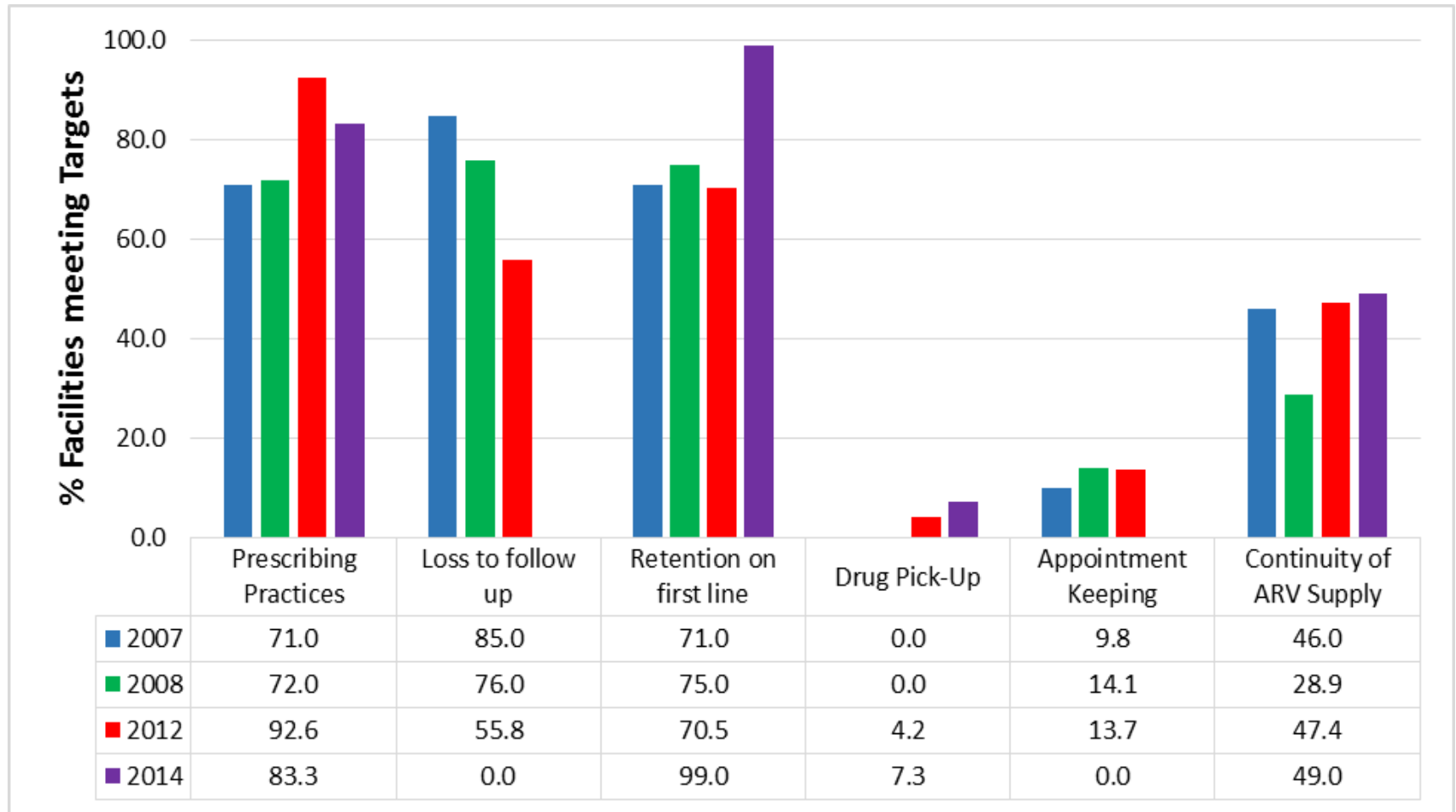
Prof. Pontiano Kaleebu
Chairperson National HIVDR committee

Cc: The Director General of Health Services
Program Manager AIDS Control Program

Early Warning Indicators of HIVDR

- Are quality of care indicators which assess factors associated with virological failure and emergence of HIVDR
- Designed to be monitored at all ART facilities as part of routine M&E
- Results provide facility specific information offering an opportunity for corrective action
- Conducted five rounds to date (2006/7, 2008/9, 2012, 2014 and 2017)

Summary of 4 rounds of EWI survey results



Recommendations and implementation

- Harmonize routine medical records to facilitate routine HIVDR Early Warning Indicator abstraction at ART facilities

12-month Retention data is now routinely collected in DHIS-2 and HMIS 106a

Viral load suppression; % of patients with viral load <1000 copies/mL 12 months after ART initiation: Incorporated into the HMIS 106a for national reporting

Recommendations and implementation

- Routine viral load monitoring for all on ART.

Routine VL monitoring started in Aug 2014

Recommendations and implementation

- VL monitoring at 6 and 12 months after ART initiation instead of 18 months

The MOH revised the VL algorithm to provide for 12 monthly VL monitoring for newly initiating individuals in the revised 2018 guidelines

Recommendations and implementation

- Standardized guidelines for assessment of adherence for tracking HIVDR and treatment outcomes

The MOH developed an adherence strategy that clearly outlines how ART adherence should be assessed and documented on the ART card

Surveys of Transmitted HIVDR

- Conducted among recently infected, ARV-naïve individuals
- The *Method* supports population-level classification of the prevalence of transmitted HIV DR in a specific geographic area into 1 of 3 categories:
 - **LOW prevalence** : < 5%;
 - **HIGH prevalence** : > 15%;
 - **MODERATE prevalence** : Between 5% and 15%

Summary of TDR

- 10 surveys/ studies conducted
- Apart from one study which had TDR prevalence >15%, the other studies had low or moderate rates of transmitted drug resistance levels

Following WHO recommendations this means where moderate rates have been identified there should be repeat surveys within the subsequent five years.

Pre-treatment DR

- DR detected in ART drug naïve people initiating ART or people with prior ART exposure initiating or reinitiating first line ART
- So it is either TDR or acquired or both
- Conducted surveys in adults and children

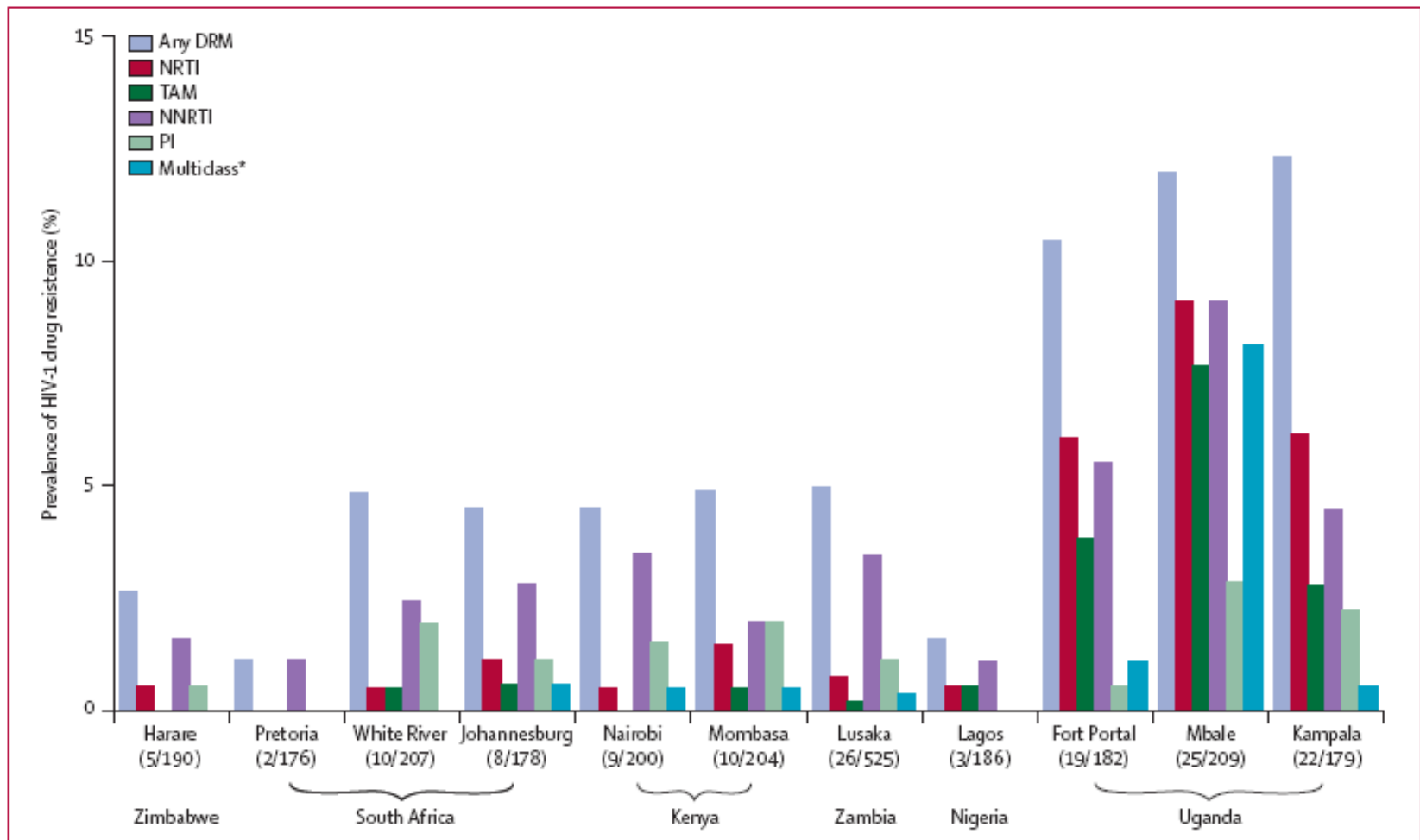
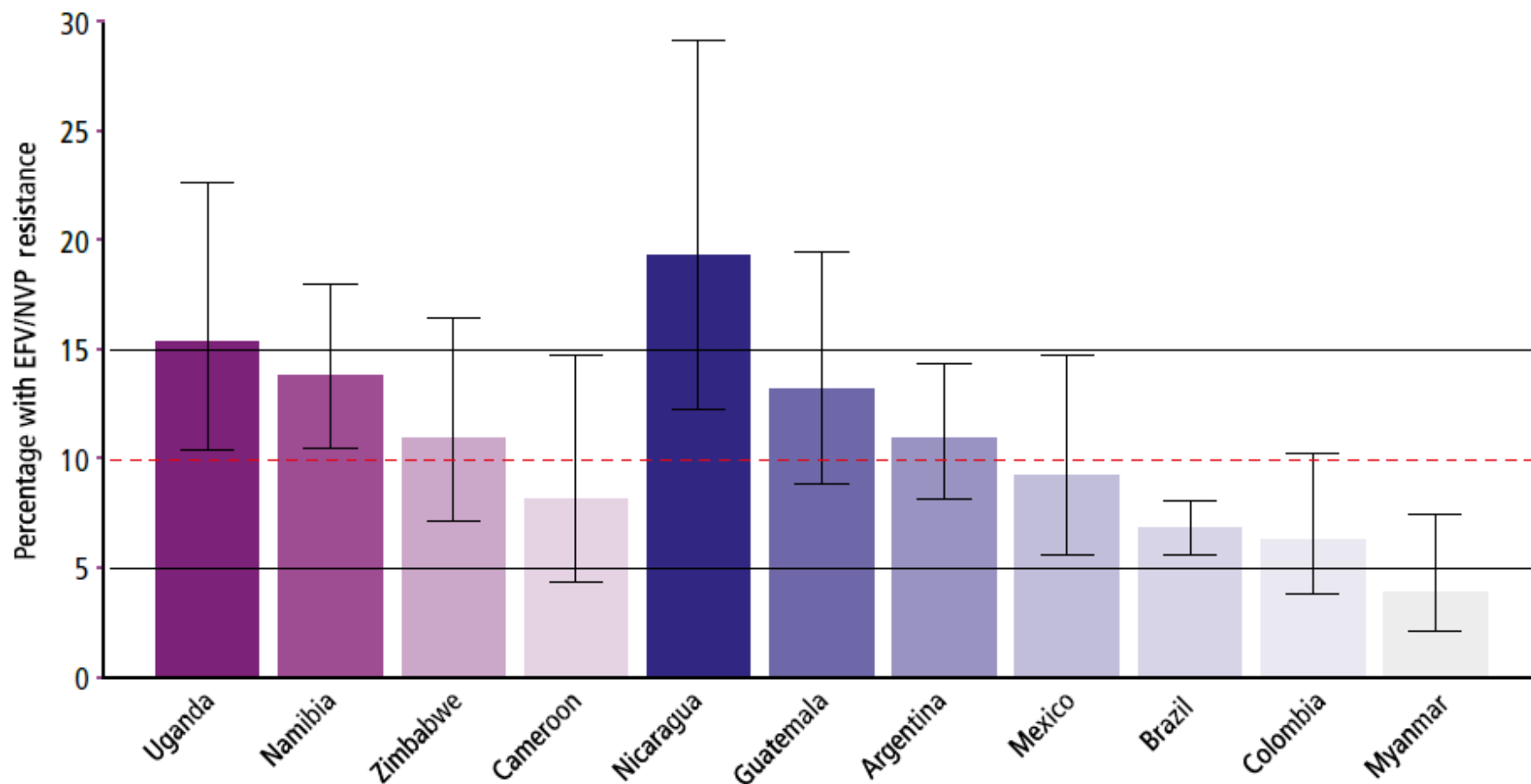


Figure 2: Prevalence of HIV-1 primary drug-resistance in antiretroviral-naïve individuals in the PASER-M cohort by region and drug class
 People with at least one drug-resistance mutation shown as proportion of all people by region and drug class. Regions are clustered by country and sorted by descending calendar year of roll-out of antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor. TAM=thymidine analogue mutation. NNRTI=non-NRTI. PI=protease inhibitor. *Multiclass is resistance to at least two drug classes.

Hamers L et al. Lancet 2011

Fig. 3.1. Pretreatment HIV drug resistance to EFV or NVP in first-line ART initiators
(Pretreatment HIV drug resistance national surveys, 2014–2016)



Resistance to EFV/NVP is defined by the Stanford HIVdb algorithm (version 8.3); sequences with predicted low-, intermediate- or high-level resistance are considered as resistant.

Recommendations and implementation

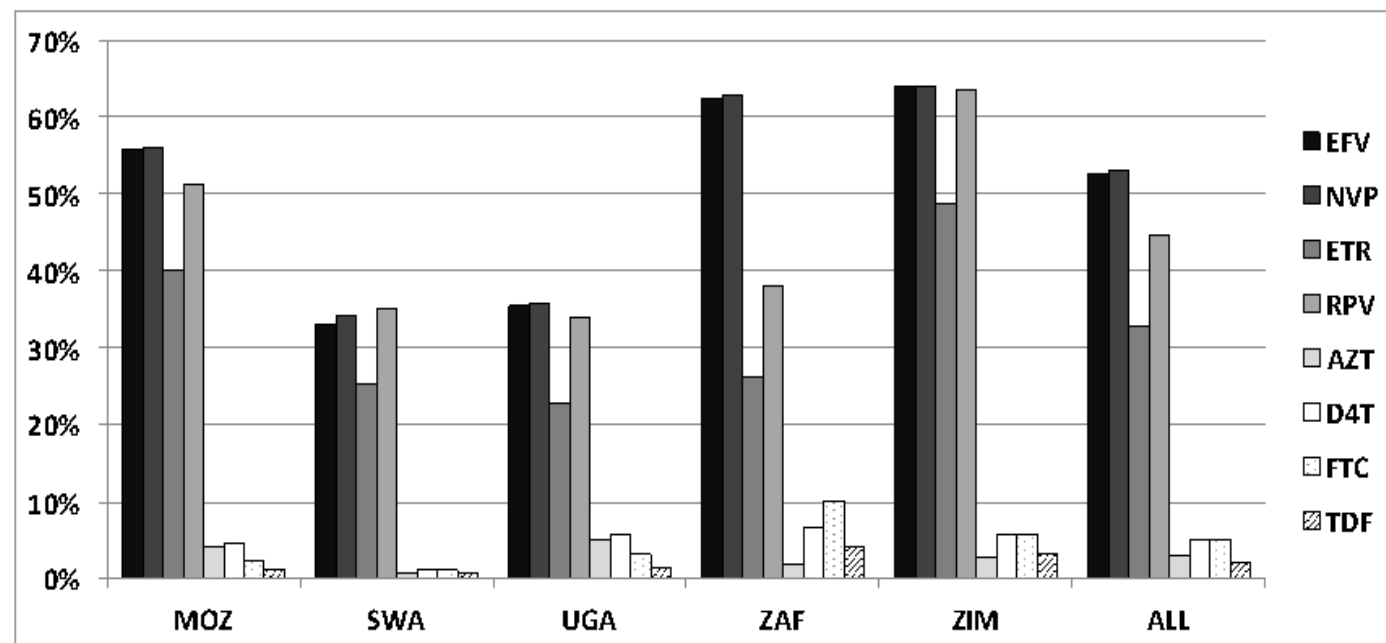
- Use of Integrase strand inhibitors (Dolutegravir) as first line due to high Pre-Treatment HIVDR to NNRTIs in the country

MOH has adopted DTG-based regimens as the preferred first line ART regimen in women >50 years, adolescent and adult men; and as an alternative second line in the above eligible groups

Pre-treatment and Acquired HIV drug resistance among children

- Completed work
 - Surveillance of initial HIV drug resistance among children <18 months recently diagnosed with HIV-completed in 2013
 - MARCH study conducted by JCRC colleagues

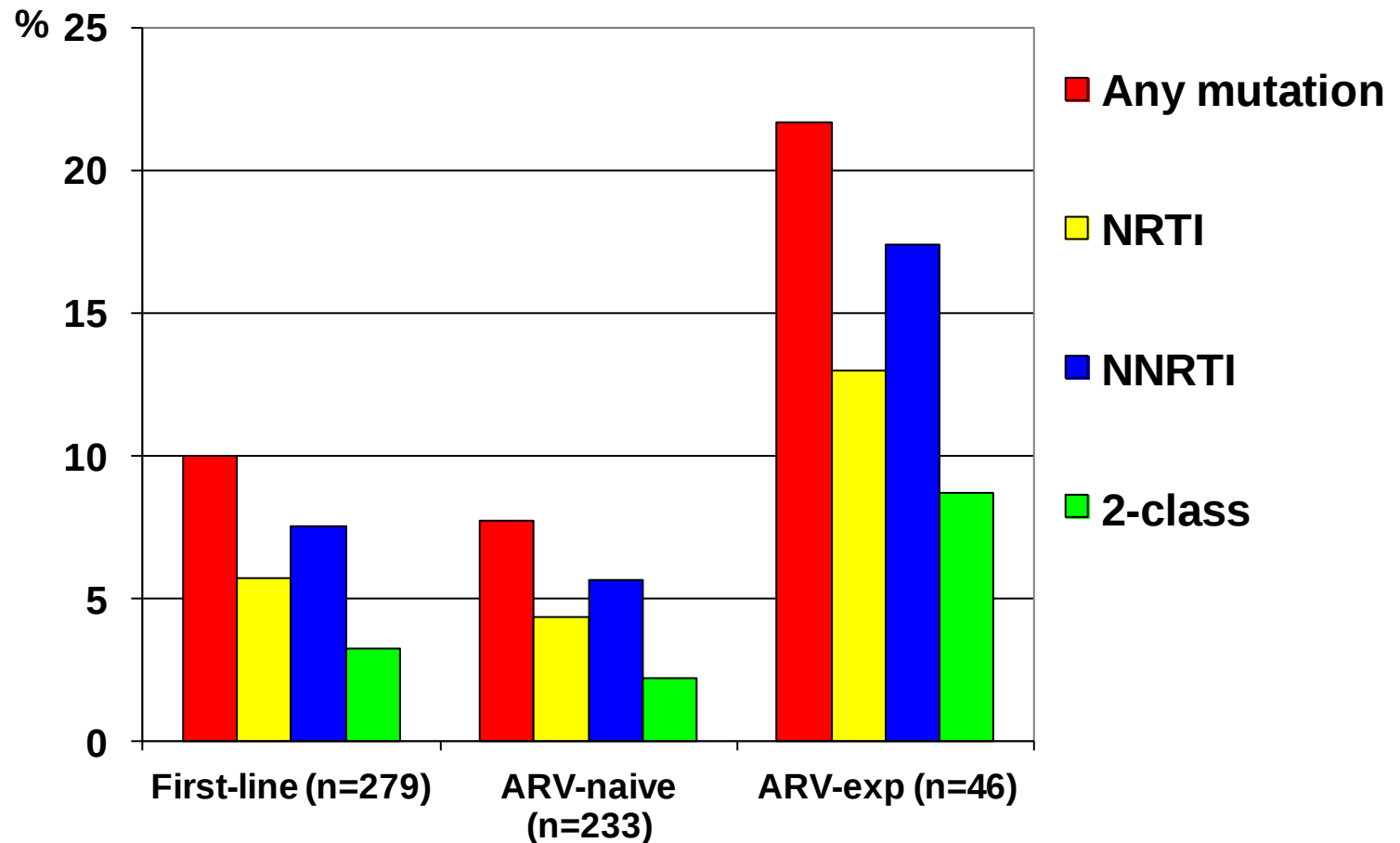
Predicted levels of NRTI and NNRTI resistance by drug



MOZ= Mozambique; SWA=Swaziland; UGA=Uganda; ZAF= South Africa; ZIM=Zimbabwe. EFV=efavirenz ; NVP=nevirapine; ETR= etravirine; RPV=rilpivirine; AZT=azidothymidine (zidovudine); D4T=Stavudine; FTC=emtricitabine; TDF= tenofovir

HIV drug resistance in African infants and young children newly diagnosed with HIV: a multicounty analysis. Jordan et al. 2017

HIVDR among children initiating first-line ART



Frequencies (%) of HIVDR mutations in patients initiating first-line treatment either ARV-naïve or with previous PMTCT (n=14) or unknown exposure status (n=32)

Recommendations and implementation

- Use of PI based regimens as first line for HIV infected infants especially with prior PMTCT exposure

MOH rolled out use of Lopinavir pellets as first line for HIV positive infants <3 years country -wide in 2016

Repeat of surveillance of initial HIV drug resistance among young children and acquired HIVDR among children and adolescents

Acquired HIV Drug Resistance at Sentinel sites

- A survey based on the WHO guidance of 2004 at 3 sentinel sites
 - Mbale RRH, Masaka RRH and Nsambya HomeCare
 - Enrolled 425 patients initiating ART and followed them up for 12 months
- Key findings
 - Baseline HIVDR was 2.1%
 - After 12 months, overall HIVDR prevalence was 9.0%
 - K65R mutations

Recommendations and implementation

- Use of Tenofovir in standard first regimens

The MOH revised the national treatment guidelines and adopted use of Tenofovir as first line in 2013

Acquired HIV drug resistance ...

- Cross-sectional survey of acquired HIVDR among adults receiving first-line antiretroviral therapy for 12 and 48 months
 - Followed WHO nationally representative sampling
 - Key findings:
 - At 12 months virological suppression was 92.5%
 - 93.3% of patients with virological failure had HIV drug resistance mutations(92.9% NNRTI; 82.1% NRTI and 3.3% had PI mutations

New recommendation under discussion

- We see high HIVDR at first VF at 12 months

Is it wise to wait for another VL at least 3 months with intensive adherence counselling before switching patients?

Second line

- Poor adherence, rather than HIV DR is driving most of the VF to second line.
- It is estimated that major protease inhibitor resistance at the time of second line VF ranges between 0 -50%.
- Our studies at UVRI, MSF, JCRC etc confirm this

Experience with resistance to second-line ART

- Cross sectional survey in MRC longitudinal cohort with 956 patients on ART for >6 months (81% on ART)
 - 119 had VL>1,000 copies/ml (36 on 2nd-line ART and only 7 had PI mutations)
- MSF-Arua Epicentre samples from (78) patients failing on second-line; 18.5% had $\geq$ major PI mutations
- JCRC PASER study: 22% (32 out of 227 patients had PI mutations)

Recommendations and implementation

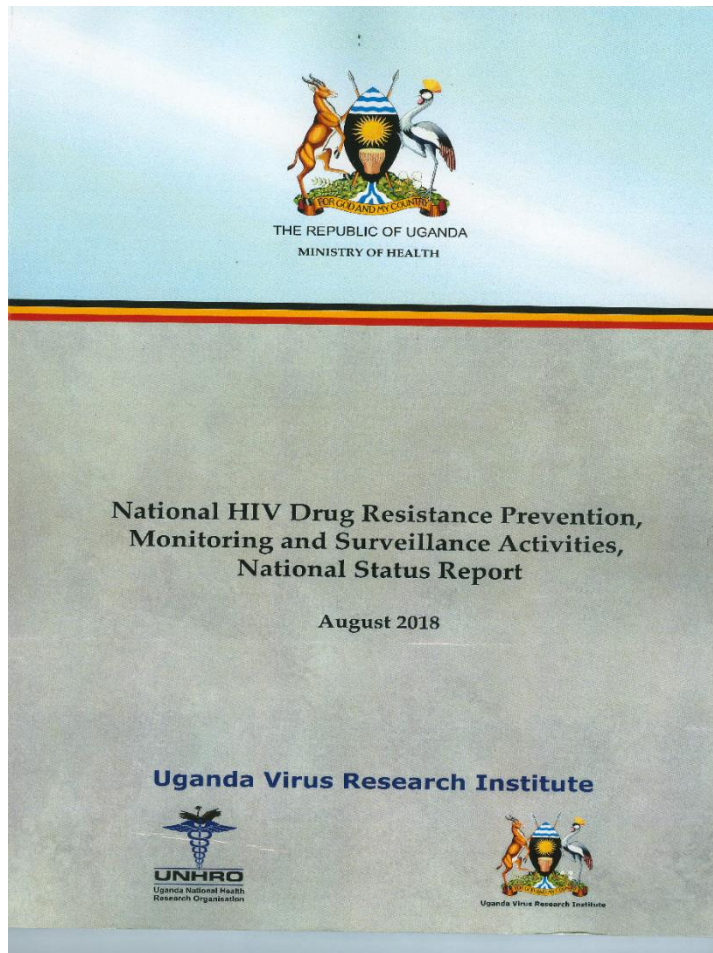
- Routine HIVDR testing for individuals failing 2nd line ART regimens

The MOH included routine HIVDR testing in the revised 2016 national guidelines at UVRI and JCRC

In addition, MOH has constituted a 3rd line committee that reviews genotype results and patient history notes to determine appropriate 3rd line drugs

HIV DR report

- Summary of achievements
- Recommendations and implementation



State Minister for Health - Sarah Opendi, CDC Uganda - Director Dr. Lisa Nelson, Director General Uganda AIDS Commission - Dr. Nelson Musooba, UVRI Director - Pontiano Kaleebu and Dr. Mugaga Kaggwa at the stakeholders meeting.

ACTION PLAN

GLOBAL ACTION PLAN ON HIV DRUG RESISTANCE 2017-2021

JULY 2017

HIV DRUG RESISTANCE



The Global Action Plan...

- Provides countries and national and international partners with a framework, which when implemented collectively between 2017-2021 will contribute to the achievements of the Fast Track global targets of 90-90-90 by 2020 and to ending the epidemic by 2030.

Way forward

- We have endorsed the WHO Global Action Plan on HIV DR
- HIVDR prevention, monitoring and surveillance activities have to be part of the ART scale up country plan
- This will require financial commitment from government and development partners
- Information generated from these activities will continue to feed into policy and practice

Acknowledgment

- Ministry of Health (ACP, CPHL and UVRI)
- CDC-Uganda
- WHO and CDC Country offices and WHO Geneva and CDC Atlanta for Technical and Financial Assistance
- Funders (CDC-PEPFAR, MRC-UK and PharmAccess)
- The Global Fund and other funders
- Members of the HIV DR working group
- Implementing Partners and Collaborating Institutions (MRC/UVRI and LSHTM, JCRC, MSF, IDI, TASO etc)
- Staff and patients at participating sites (hospitals and health centers) that participated in the surveys
- Reference labs at UVRI and JCRC

THANK YOU