



Botswana Ministry of Health

Department of HIV/AIDS Prevention & Care
**ARV Drug Resistance Surveillance
Treatment Failure Management**
**4th South African
HIV Drug Resistance Workshop**

Dr. Diana Dickinson
30 October 2009



Primary Resistance Surveillance

Ambitious ARV therapy scale up in African Countries including Botswana has raised concern of generating a transmitted drug resistance epidemic.

Further uncertainty about the possible behavior of HIV-1C under ARV pressure required regular monitoring of the evolution of transmitted HIV-1C drug resistance.



Primary Resistance Surveillance

Primary Transmission is dependant on a number of factors including:

- ARV Coverage of the area
- Length of exposure
- Proportion of ARV patients failing tx
- % of failure with various R strains
- Amount of time patient remain on failing regimens



Primary Resistance Surveillance

Attention to the monitoring of HIV DR was a focus of the ARV program from its inception

- 2001 HIV Sentinel Surveillance
Results: No significant transmitted ARV DR
- 2005 HIV DR Threshold Survey
Results: Francistown <5%, Gab not determined
- 2007 HIV DR Threshold Survey
Results: Minor Mutations in 5 samples
(4 reported to not be on ARVs) FT & Gabs <5%



Secondary Resistance Surveillance

ARV Failure Management Protocol

All clinicians who manage patients on ARV at IDCC are responsible to monitor viral load response on each and every office visit.

- ✓ VL schedule no baseline, 3 months and every 6 months thereafter
- ✓ Pediatric- no baseline and every 3 months

Definition of Suboptimal Viral Load Suppression

- Viral load > 400 copies/ml after six months on HAART
- Viral load > 400 copies/ml after a documented < 400 copies/ml during their course on HAART



Sub-Optimal Viral Suppression

A patient who satisfies the following should be managed as follows:

- MD/Nurse assessment
- Priority viral load drawn
- MD/Nurse assessment
- Priority viral load drawn



Current Protocol Failure Management and Drug Resistance Protocol

- All ARV Clinics have provision for on-going monitoring of viral loads (3m post initiation and every 6m thereafter, Pediatrics every 3 m)
- Out of range viral loads more easily identified (as baseline viral loads eliminated in 2008 to improve abnormal result tracking)
- Adherence support provided by specially trained staff (KITSO Medication Adherence Course)
- All second line failures are eligible for resistance testing with Specialist MD referral care available



Training

On-going training and mentorship in Failure Management as part of PEPFAR Master Trainers mandate

On-going Site Director's Meetings with updates on Failure Management and statistics sharing

Revision of KITSO Resistance Lectures for new Resistance Surveillance Course completed by Dr. Florence Doualla-Bell. Pilot to be held in November.



Program Monitoring

Routine feedback provided to the ARV **Clinical Guidelines Committee** and to the **Drug Forecasting and Costing TWG**

to determine and improve upon the treatment program policy, priorities and outcomes

Triangulation Plus : CMS / IPMS&PIMSII / Failure Mgt / Master Trainers / EWI



Monitoring

First systematic chart review (2004) for Adult 1st line failure rates completed at PMH-IDCC

4811 patient charts = **3.5%**

66% private sector referrals

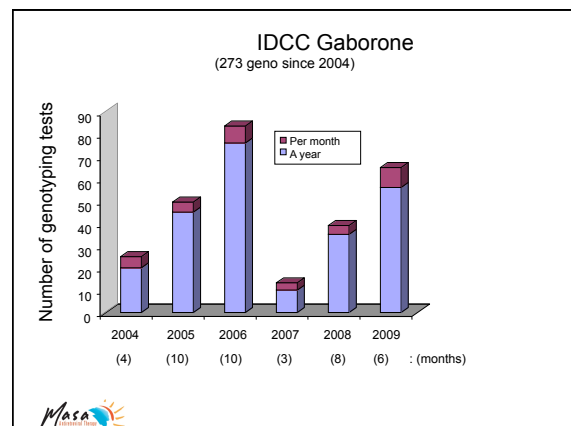
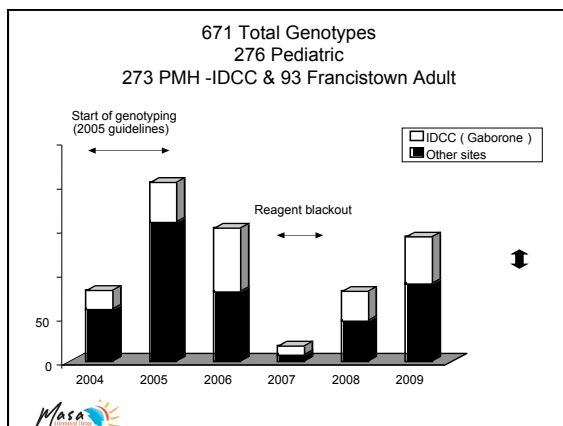
Five Year Review completed PMH-IDCC (2002-2007)

11,683 patient charts = **3.6%**

44% private sector referrals

National Site Directors Reporting (July 2009)

48,558 patients reported (40 clinics) = **2.18%**



Secondary Surveillance Monitoring

Early Warning Indicators Pilot Project

16 sites selected in December 2008
All indicators above WHO recommendations

PEPFAR Master Trainers Site Support Visits

On-going chart reviews on Site with
Pediatric Training provided by Baylor

Site Director's Monthly Reports



WHO Early Warning Indicators Pilot

ART Prescribing Practices:

% of patients initiating ART at the site during a selected time period who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line regimen

Suggested Target: 100%

Botswana Pilot outcome: 100%



WHO Early Warning Indicators Pilot

Patients Lost of Follow Up

% of patients initiating ARV at the site in selected time period who are lost to follow up during the 12 months after starting ARV

Suggested Target: <20%

Botswana Pilot outcome: 7.46%



WHO Early Warning Indicators Pilot

Patient Retention of First-Line ARV

% of patients initiating ARV at the site during a selected time period who are taking an appropriate first-line ARV regimen 12 months later

Suggested target: >70%

Botswana Pilot outcome: 89.12%



WHO Early Warning Indicators Pilot

ARV Clinic Appointment-keeping

% of patients initiating ARV at the site during a selected time period who attended all clinic appointments on-time during the first 12 months on ARVs (Medi-tech sites only)

Suggested target: >80%

Botswana Pilot outcome: 81.94%



WHO Early Warning Indicators Pilot

Drug Supply Continuity

% of quarters in a designated year in which there were no ARV drug stock-outs.

Suggested target: 100%

Botswana Pilot Outcome: 100%



WHO Early Warning Indicators Pilot

Viral Load Suppression

% of patients initiating ARV at the site in a selected time period whose viral load is <400 copies/ml after 12 months of 1st line ART

Suggested target: >90%

Botswana Pilot outcome: 95.66%

Deaths Within the First Year on ARV

Botswana Pilot outcome: 6.48%



Resistance Surveillance Research

Resistance Surveillance Strategic Plan

National Research priorities include:

- Analysis of secondary resistance Mutational Profiles – Adults & Peds
- Outcomes of empiric treatment switch vs genotyping post 2nd line failure
- Mutational profile of 1st line failure (Atripla, TDF/FTC, NVP)
- Ultra-sensitive testing (1' & 2')



Five Year Follow Up of Genotypic Resistance Patterns in HIV-1 Subtype C Infected Patients in Botswana after Failure of thymidine analogue-based regimen

Florence Doualla-Bell, T. Gaolathe, A. Ayalos, S. Cloutier, N. Ndwapi, C. Holcroft, H. Moffat, D. Dickinson, M. Essex, M. Wainberg, M. Mine

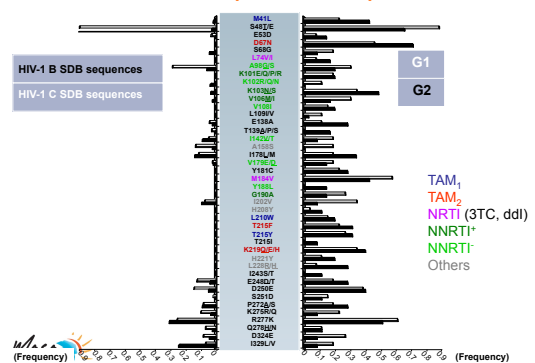
Objective: To establish genotypic resistance profiles among the 3.6% patients who experienced virologic failure while being followed within Botswana's ARV Therapy Program between 2002 – 2007.

RESULTS:

Any Resistance to PIs	78%
Any Resistance to NRTI	87%
Any Resistance to NNRTI	90%



Frequency Mutations/Polymorphisms in Reverse Transcriptase



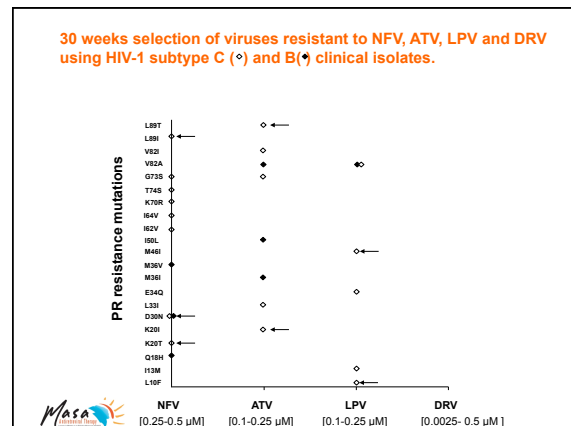
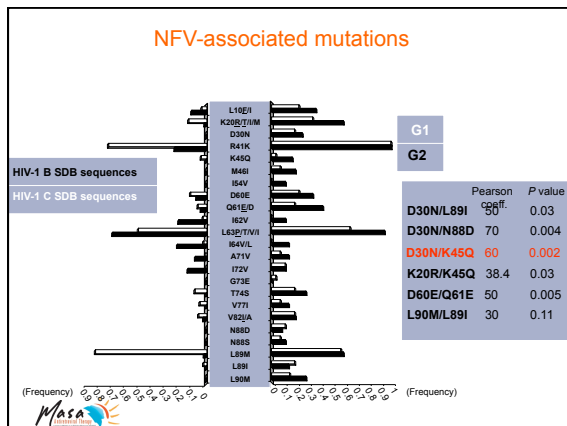
Frequency of expected HIV-1C RT Mutations (%)

NRTI mutations		G1 (n=26)	G2 (n=37)		
M184V		61	40.5		
K65R		7.7	0		
L74V		7.7	16.2		
TAM ₁	41L	26.9	40.5	TAM ₁ 0	50%
	210W	19.2	18.9	TAM ₁ 1	19%
	215Y	26.9	29.7	TAM ₁ 2	19%
				TAM ₁ ≥3	12%
TAM ₂	67N	46	67.6	TAM ₂ 0	46%
	70R	35	37.8	TAM ₂ 1	12%
	215F	26.9	29.7	TAM ₂ 2	8%
	219Q	34.6	37.8	TAM ₂ ≥3	34%
					38%
NNRTI mutations					
K103N		34.6	48.6		
V106M		30.8	16.2		
Y181C		23	27		
G190A		23	13.5		

NNRTIs

	G1		G2		
	EFV (n=14)	NVP (n=12)	EFV (n=21)	NVP (n=16)	
A98S/G	2	5	3	4	
K101E/Q/PIR	2	3	4	4	21%
K102R/Q/N	3	1	0	0	
K103N	5	4	13	5	43%
V106M	7	1	4	2	22%
I135V/T	5	3	9	8	40%
V179E/D	3	1	2	3	
Y181C	0	6	2	8	25%
	1	5	2	3	17%

	G1	G2
0	20%	11%
1-2	53%	57%
3-4	23%	32%
5	4%	0%



Our results highlight the fact that resistance is a complex phenomenon involving not only conventional points of mutation but also associations of mutations which are not taken into consideration by standard algorithms

We described a new pathway for NFV resistance involving the **K45Q** mutation

Specific mutation may be the result of specific pharmacological pressure, i.e. **L74V, I202V, H221Y, L228R/H, K45Q**

These results demonstrate the possible interplay between the different classes of inhibitors, i.e. NNRTI (**G190A**) and NRTI (**TAM₁**)

Finally, in terms of future perspective, our *in vitro* results suggest the promising role of DRV and its potential as the PI of choice in naïve patients (*Ref. Artemis study*).

Challenges

Pediatrics and Adolescents

Current failure rates are considerably higher than adults

Fortunately, most failures are associated with poor adherence rather than resistance (no child has qualified yet for Raltegravir treatment based on genotyping results)

Drug resistance survey research project to be launched by U Penn and Baylor

FAILURE & SECONDARY RESISTANCE SURVEILLANCE TEAM

Tendani Gaolathe, MD	tendaniq@yahoo.com	267-7211-1501
Ava Avalos, MD	avaavalos@gmail.com	267-7211-6222
Suzanne Cloutier, MSPH	suzcloutier@yahoo.com	267-7131-5967
Ndwapi Ndwapi, MD	ndwapi@it.bw	267-7210-1014
Dr. Bakae	odirileb@yahoo.com	267-7120-4904
Florence Doualla-Bell, PhD	fdoualla@ldi.igh.mqill.ca	267-7144-5637
Madise Mine, PhD	mmine@hbp.org.bw	267-7130-7122
Mark Wainberg, PhD	mark.wainberg@mcqill.ca	514-340-8307
Howard Moffat	hmoffat@gov.bw	267-71306174
Max Essex	messex@hsph.harvard.edu	

Many Thanks