New treatments and approaches to Tuberculosis

Tuberculosis Symposium – Eastern Europe and Central Asia

RA Ministry of Health and Médecins Sans Frontières

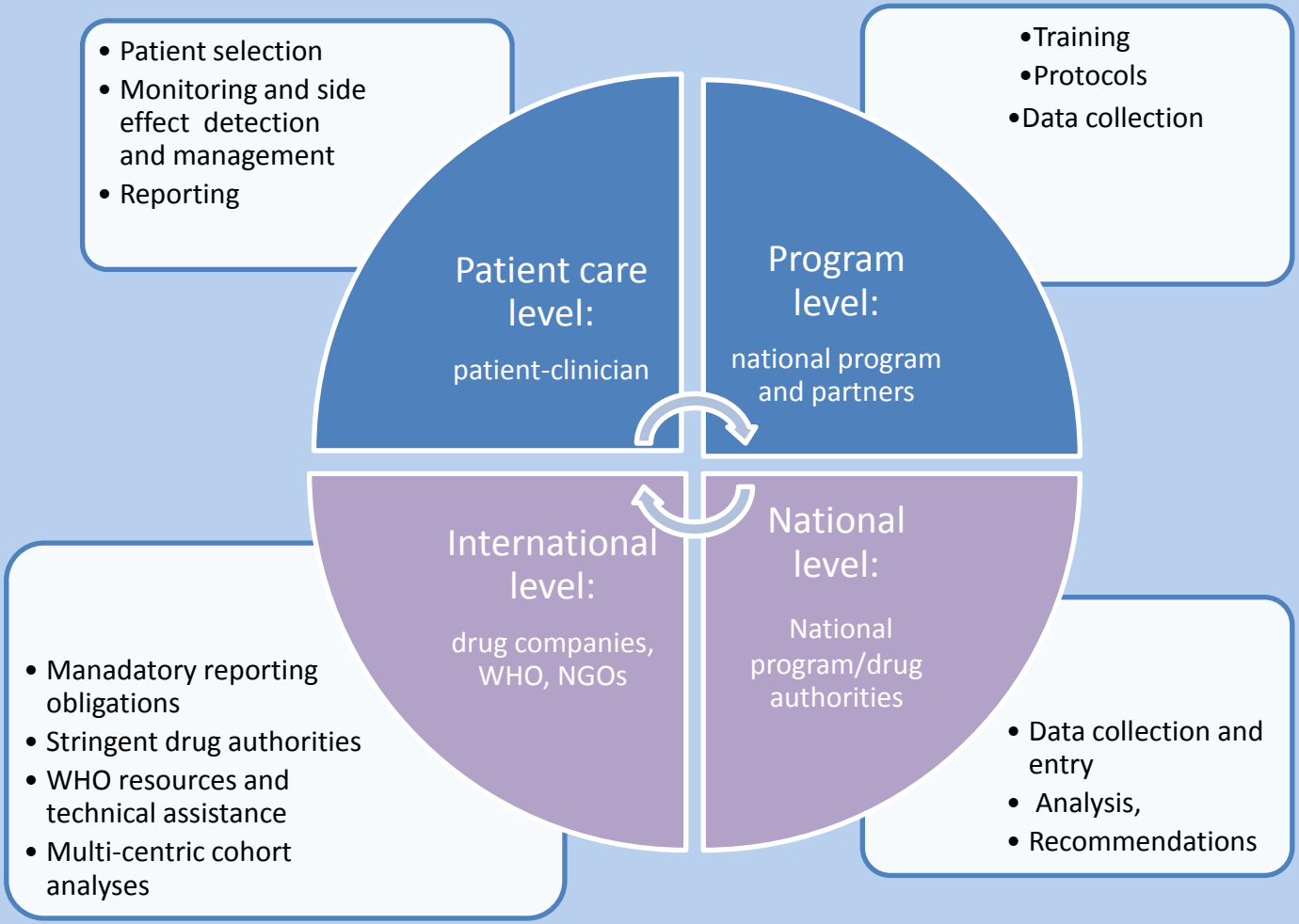
Practical experience of pharmacovigilance of investigational and repurposed drugs use in Armenia

Dr Catherine Hewison

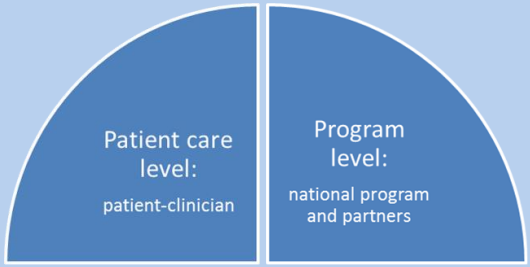
TB Referent, MSF OCP

NTC Armenia , MSF France

Pharmaco-vigilance: where does it happen, who does it?



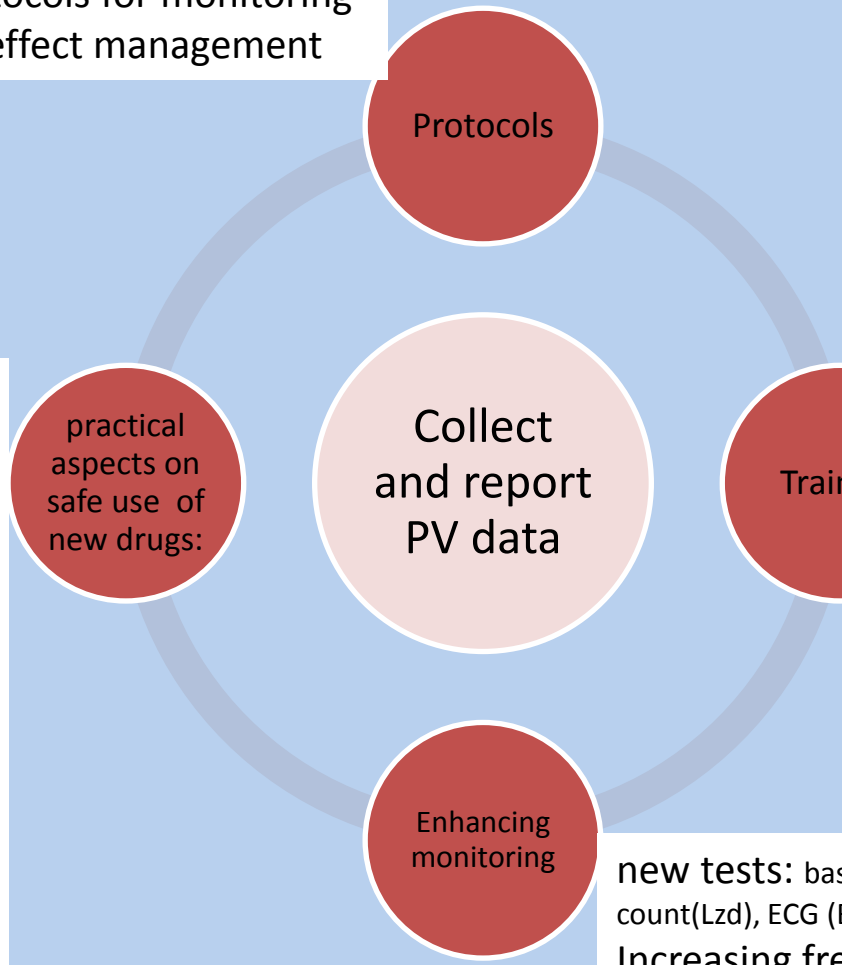
Existing system in Armenia before introduction of new drugs



- Routine monitoring and evaluation in place as part of an established DRTB program
- Functional system at patient care level:
  - Close follow-up for early detection and aggressive management of undesirable side effects
  - Standard data collection forms for reporting of routine monitoring and side effects
  - data base tool (Koch6 for MSF and eTB manager for NTP) in place
- Technical advice available from TB referent at HQ level and MSF-PIH compassionate use committee for the use of investigational drugs (CU committee)

Steps in introduction of new drugs at patient-clinician level and program level

Clear protocols for monitoring and side effect management



Training and supervision of Health staff

How to reduce possible risks and address adverse events: simple algoythms, supplementary investigations, involvement of specialists

Referral system between TB structures and other facilities /specialist; established and maintained.

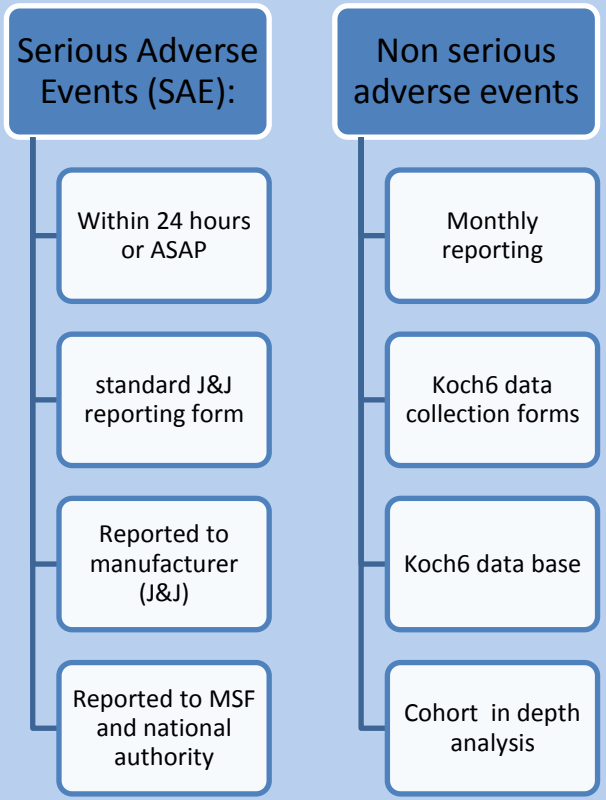
Use of expert advice from CU committee on difficult side effects/cases

new tests: baseline lipase(bdq), monthly full blood count(Lzd), ECG (Bdq, Cfz, Lfx, Mfx),

Increasing frequency (audiometry, neurological examinations, hepatic function)

Collect and report PV data

- Adaptation of data collection tool (Koch 6):
  - include new drugs
  - new fields of monitoring (lipase, ECG)
  - grading of side effects
- Additional training of staff on PV :
  - Serious Adverse Events (SAE): Definitions, monitoring, detection and management
  - Non serious adverse events: Reporting of side effects of interest for new drugs*



*Data collected: Any side effect requiring stopping a drug(temporary >2 days or permanently), Any « major » side effect (eg renal, hepatic, auditory), Any side effect of interest (eg neuropathy), All monitoring parameters of interest (ТБ Симпозиум Министерство Здравоохранения и ВБГ Центральная Азия и Восточная Европа, ТВ Symposium Ministry of Health and MSF

Practical approaches to challenges at patient care level

Challenges	Contributing factors	Approach to improvement
Causality assessment	Not always easy: multiple drug combinations, previous drug complications, co-morbidities, common side effects amongst drugs, TB	Technical support from CU committee, PV unit, TB referent, WHO Referral system with specialists and investigations (eg. EMG)
Identifying SAEs rapidly	Delays due to geographical constraints, nature of disease not always apparent	Feedback and ongoing supervision and training
Knowledge and skills of Drs in detecting and managing side effects	Concern/fear among clinicians – new to PV, less knowledge on new drugs, interactions and side-effects Vertical qualifications of Drs	Training of all staff (detection, reporting, management), protocols and algorythms Drs encouraged to develop skills(ECG reading, neurological examination) Regular supervision of treatment sites Technical support from CU committee Strengthening referral system to non TB facilities/ external specialists
Patient- Dr interaction	Sometimes not easy for clinicians to answer patients questions	Strengthening health education and counselling for patients
Analyses of data quality	Experience limited on PV for investigational drugs in MSF/ Nationally	To be developed through analysis of data and feedback to clinicians

Pharmacovigilance on new drugs are programmatic and national level

National level:

National program/drug authorities

Challenges	• First time CU treatment program introduced in the country • Unfamiliarity with reporting requirements to the drug company. • Unavailability of national protocol on PV for investigational drugs. • Lack of required diagnostic, screening equipment's/ materials and expertise at TB treatment site (ei ECG)
Approach to challenges	• National Pharmacovigilance unit is functional in the framework of Armenia Scientific Center of Drug and Medical Technology Expertise. • Spontaneous reporting system in place for all medications including anti TB drugs. • Advanced pharmacovigilance new for National PV unit • Active reporting system on Bdq use only functional since Dec 2014 with Technical support from WHO.

Practical challenges and approaches to PV for MSF

Challenges

- Enhanced PV new to MSF
- Guidelines on PV available not put into practice previously
- Identified need for a PV unit for field support and data analysis but not yet in place
- MSF field pharmacists not experienced in PV
- CU and reporting requirements also new to MSF

Approach to challenges

- Maintain regular technical support from MSF-PIH expert group
- Develop PV unit- technical support and centralisation of reporting
- Work hand in hand with clinicians in in patient level care including:
  - Strengthening the referral system to non TB facilities/ external consultants
  - Strengthening Health education and counselling for patients under new treatment.

Practical data from Armenia

Serious Adverse Events reported (N=53 patients started on new drugs)

Patient	SAE	Relation to Bdq	Outcome at end of Bdq	Final outcome
CUM002	Suspected MI and heart failure	Unlikely	Completed Bdq, culture positive	Deceased due to tuberculosis and chronic heart disease
CUY008	Severe tuberculosis and late stage cor-pulmonale	Unrelated	Bdq stopped due to severe medical condition and not completed,	Deceased due to tuberculosis
CUY0012	Severe tuberculosis, cor-pulmonale MI and heart failure	Possible	Completed Bdq, culture positive	Deceased due to hemoptysis
CUY0017	Prolonged QT	Highly likely	Finished Bdq, remains negative	Still on treatment

Lessons learnt: Not very common: not always easy to ID: could some have been missed?
Simple in theory but: some late reporting(not within 24 hours)
Followup reporting not routinely done until prompted
Assessment of causality and outcome needs support

Side effects: Patient example

Month	Date	E	H	R	Z	S	Am	Cm	Km	Lfx	Mfx	Ofx	Cs	Eto	PAS	Pto	Bdq	Lzd	Month	Date	Smear	Cult	Num
0	14/06/2013	1600			2000			1000		750			750		8000		400	600	-6	10/12/2012	S++	C+	832
1	28/06/2013	1600			2000			1000		750			750		8000		200	600	1	19/06/2013	S-	C+	1807
4	01/10/2013	1600			2000			1000		750			STOP		8000		200	600	2	15/07/2013	S-	C-	2055
5	31/10/2013	1600			2000			1000		750			750		8000		200	600	2	13/08/2013	Scanty	C-	134
6	30/11/2013	1600			2000			1000		750			750		8000		STOP	600	4	27/09/2013	S-	C-	148
9	08/03/2014	1600			2000			STOP		STOP	400		750		8000			600	5	21/10/2013	S-	C-	158
11	26/04/2014	1600			STOP						400		750		8000			600	6	27/11/2013	S-	C-	166
11	30/04/2014	1600			2000						400		750		8000			STOP	7	24/12/2013	S-	C-	183
12	16/05/2014	1600			2000						400		750		8000			600	8	20/01/2014	S-	C-	12
12	22/05/2014	1600			STOP						400		750		8000			600	8	10/02/2014	S-	C-	26
14	30/07/2014	1600									400		750		8000			STOP	10	21/03/2014		C-	46
14	13/08/2014	1600									400		750		8000			600	11	28/04/2014		C-	51
19	17/12/2014	1600									400		750		8000			STOP	12	10/06/2014	S-	C-	89
19	25/12/2014	1600									400		750		8000			600	14	29/07/2014	S-	C-	122
																			15	25/08/2014	S-	C-	130
																			16	23/09/2014	S-	C-	149
																			17	20/10/2014	S-	C-	158
																			18	24/11/2014	S-	C-	172

Month	Date	E	H	R	Z	S	Am	Cm	Km	Lfx	Mfx	Ofx	Cs	Eto	PAS	Pto	Bdq	Lzd
-6	10/12/2012	S	R	R	R	R	S	S	-			R	-	R	-			
-6	10/12/2012		R	R														
1	19/06/2013						S	S	-			R	-	R	-			
2	15/07/2013																	

Z stopped twice due to arthralgia, Lzd stopped 3 times due to thrombocytopaenia
Both known side effects: management of the side effects important but is it PV?
Patient now at 20 months of treatment, culture negative

Side effects: Routine collection of data (non serious events) n=53 patients

40 patients reported side effects	127 side effects
neurotoxicity or CNS effect	29
gastrointestinal effect	24
Cardiac/ECG	18
hepatotoxicity	13
other (Mg, lipase, blood pressure)	12
hematologic effect	7
systemic hypersensitivity reaction	7
nephrotoxicity	6
ototoxicity	5
dermatologic reaction	3
musculoskeletal effect	2
ophtalmic toxicity	1

Areas to improve:

- Grading not done No details on non TB drugs (self prescribed, co-morbidities, side effects drugs, homepathic)
- Which drug caused the problem?
- Many known side effects, is it pharmacovigilance?
- Alot of information, how useful?

Treatment changes and interruptions due to side effects: Patient example

Month	Date	E	H	R	Z	S	Am	Cm	Km	Lfx	Mfx	Ofx	Cs	Eto	PAS	Pto	Amx-Clv	Bdq	Cfz	ImpCln	Lzd	Month	Date	Smear	Cult
0	19/06/2013									1000			750				2000	400	300	2000	600	-10	15/08/2012	S+	C+
1	13/07/2013									1000			750				2000	200	300	2000	600	-3	21/02/2013	S++	C+
3	27/08/2013									1000			750				2000	200	100	2000	600	0	11/06/2013	S++	C+
5	31/10/2013									750			750				2000	200	100	2000	600	2	19/07/2013	S-	C-
5	01/11/2013	Stp	Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	3	20/08/2013	Scanty	C-
5	05/11/2013									750			750				2000	200	100	2000	600	5	23/10/2013	S-	C-
6	29/11/2013	Stp	Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	6	02/12/2013	S-	C-
6	16/12/2013									750			750				2000	200	100	2000	600	8	29/01/2014	S-	C-
6	18/12/2013	Stp	Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	9	27/02/2014	S-	C-
6	21/12/2013									750			750				2000	200	100	2000	600	10	27/03/2014	S-	
7	23/12/2013									750			750				2000	200	100	2000	STOP				
7	27/12/2013									750			STOP				2000	200	100	2000	600				
8	30/01/2014									750			750				2000	200	100	2000	600				
9	20/02/2014									750			750				2000	STOP	100	2000	600				
12	09/06/2014	Stp	Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp	M-Stp				
12	17/06/2014									750			750				2000		100	2000	600				
Month	**Date**	**E**	**H**	**R**	**Z**	**S**	**Am**	**Cm**	**Km**	**Lfx**	**Mfx**	**Ofx**	**Cs**	**Eto**	**PAS**	**Pto**	**Amx-Clv**	**Bdq**	**Cfz**	**ImpCln**	**Lzd**				
-10	15/08/2012	R	R	R	R	R	R	R	-			R	S	S	S										
-3	21/02/2013						R	R	-			R	S	R	S										

- 4 total treatment interruptions due to side effects
- 2 treatment changes due to side effects (Lzd: neuropathy, Cs: syncope)

Treatment changes and interruptions due to side effects: routine collection of data (n=53)

115 treatment changes of individual drugs related to side effects , in 38 patients			
26 treatment interruptions (all treatment stopped) temporarily due to side effects (>2 days), in 14 patients			
182 treatment changes due to side effects by drug (> one drug may be changed in one treatment change)			
Number of changes by drug	Bdq	19	
	lzd	64	(1 permanent)
	Ipm	13	
	Cfz	36	(1 permanent)
	Amox-clav	5	
	Pto	7	
	Cs	13	
	Km/Cm	20	
	Lfx	5	

Challenges: How to analyse this data? Bias in data collection for new drugs versus « old », not easy to identify the drug causing the problem

Areas to improve: Grading not done, No details on non TB drugs (self prescribed, co-morbidities, side effects drugs, homepathic), permanent changes not permanent until end of treatment.. therefore not coded as such, effects of co-morbidites important and not always clear in data

Conclusion 1

2 areas of PV can develop in parallel at 2 different speeds:

1. **Patient and program level:**
   - introduction on new drugs safe and possible with support
   - Staff's knowledge and skills improves quickly once familiar with drugs
   - Less side effects than usual drugs

2. **National and international level**:
   - requires planning, capacity building and budget over many years

- Access to new drugs possible and safe whilst national PV system being developed
- Mutually supportive

Conclusion 2

Collection of ALL data in ALL patients:

- Resource heavy to collect (better to spend resources on medical care)
- Heavy to analyse
- Quality of data important to give meaning

Pharmacovigilance is not just recording known side effects

- Need to concentrate on new unknown adverse events

- Concentrating energy at sentinel sites will be able to produce early and good quality signals
  - Eg end TB sites