

Management of Adverse reactions events in the treatment of MDR-TB

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Presentation outline

- Monitoring of adverse reactions
- Strategies for management of adverse reactions
- Frequency of adverse reactions associated with second line drugs

Definitions

- **Allergic reaction:** IgE - mast cell - histamine axis; may be mild (itching, rash) or fatal (anaphylaxis)
- **Toxic effect:** tissue or organ injury or damage (functional or structure), that may lead to irreversible harm or death if not managed properly
- **Side effect:** reversible, unpleasant but not intrinsically dangerous reaction to drug (unless prolonged, untreated)

Monitoring of adverse drug reactions

- Monitoring of drug side effects should be provided **full course of treatment**
- **Daily** observation by DOT provider,
- Monitoring for adverse effects **monthly**
- Patients should be **informed** about side effects
- All side effects should be **registered**

Monitoring Schedule

- Daily check during DOT –
 - Symptoms of allergy,
 - side effects,
 - adverse drug reactions (ADRs)
- Monthly clinical evaluation by MD: examination for symptoms and signs of ADRs
 - skin rash due to drug allergy
 - bedside tests of hearing (audiometry) and vision (color, visual fields, acuity)
 - dehydration, malnutrition due to anorexia, vomiting, diarrhea
 - abdominal tenderness, jaundice due to hepatotoxicity

Monitoring Schedule

- Monthly clinical evaluation by MD, continued:
 - dry skin, slow reflexes, eyelid lag due to thyrotoxicity of ETA/PTA, PAS
 - muscle cramps, palpitations, fluid retention due to nephrotoxicity of aminoglycosides
 - Mental status examination, sleep disturbances due to CNS effects of cycloserine, quinolones
 - tenderness in joints, connective tissue due to quinolones

Monitoring Schedule

- Monthly lab tests during intensive phase
 - Creatinine, electrolytes (Serum potassium) at baseline, then at least monthly while receiving an injectable drug
 - liver enzymes,
 - optometry, audiometry, electrocardiography
- Quarterly throughout
 - liver enzymes, (electrocardiogram), (depression inventory)
- Otherwise, depending on patient-specific side effects and drug toxicity
 - Thyroid stimulating hormone TSH (FT_3 , FT_4), - At baseline and at, ideally once between months 6-9 if receiving ethionamide and/or PAS; and monitor for signs/symptoms of hypothyroidism
 - uric acid

Management of adverse reactions - standard protocols for registration - 4

Registration of adverse reactions form

Patient name..... Name of the institution.....
Physician.....

Repeat measurements monthly (after intensive phase every three months)

Adverse reaction	Date	Regimen	Adverse reaction related drug	Treatment of adverse reaction	Monitoring

Strategies for management of adverse reactions

Side effects may be different by the severity

- **Mild** - treatment regimen not changed
- **Moderate** – interruption of causative drug or all drugs for short time
- **Severe** – discontinuation of causative drug

Life threatening adverse events

- Anaphylaxis
- Severe toxic allergic reactions (exfoliative dermatitis, Steewen-Johnson syndrome)
- Severe gastritis with bleeding
- Severe hepatitis
- Renal failure
- Severe electrolytes disturbances

Specific trainings on adverse events to second-line drugs

- Ensured training and education based on task analysis for HCW
- Ongoing patient education is provided
- Compliance with MDR-TB treatment of staff and patients achieved
- Good communication and psychosocial support for patients

Management of adverse reactions

- Altering dosages when appropriate
- In case of need discontinuation of some drugs
- Avoid of additional drug resistance development during management of side effects

Use of ancillary drugs to treat adverse events

Indication	Drug
Nausea, vomiting, stomach upset Heartburn, sour stomach, ulcer	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate, H ₂ -blockers and proton pump inhibitors etc.
Oral candidiasis	Fluconazole, clotrimazole
Diarrhea	Loperamide
Cutaneous reactions, itching	Hydrocortisone cream, calamine, aladryl lotions, Antihistamines, steroids (prednisone, dexamethasone)
Systemic hypersensitivity reactions	oral steroids (prednisone), injectable steroids (dexamethasone, methylprednisolone)
Bronchospasm	Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids, (beclomethasone, etc.),
Hypothyroidism	Levo-thyroxine
Electrolyte wasting	Potassium and magnesium replacement

Use of ancillary drugs to treat adverse events - continue

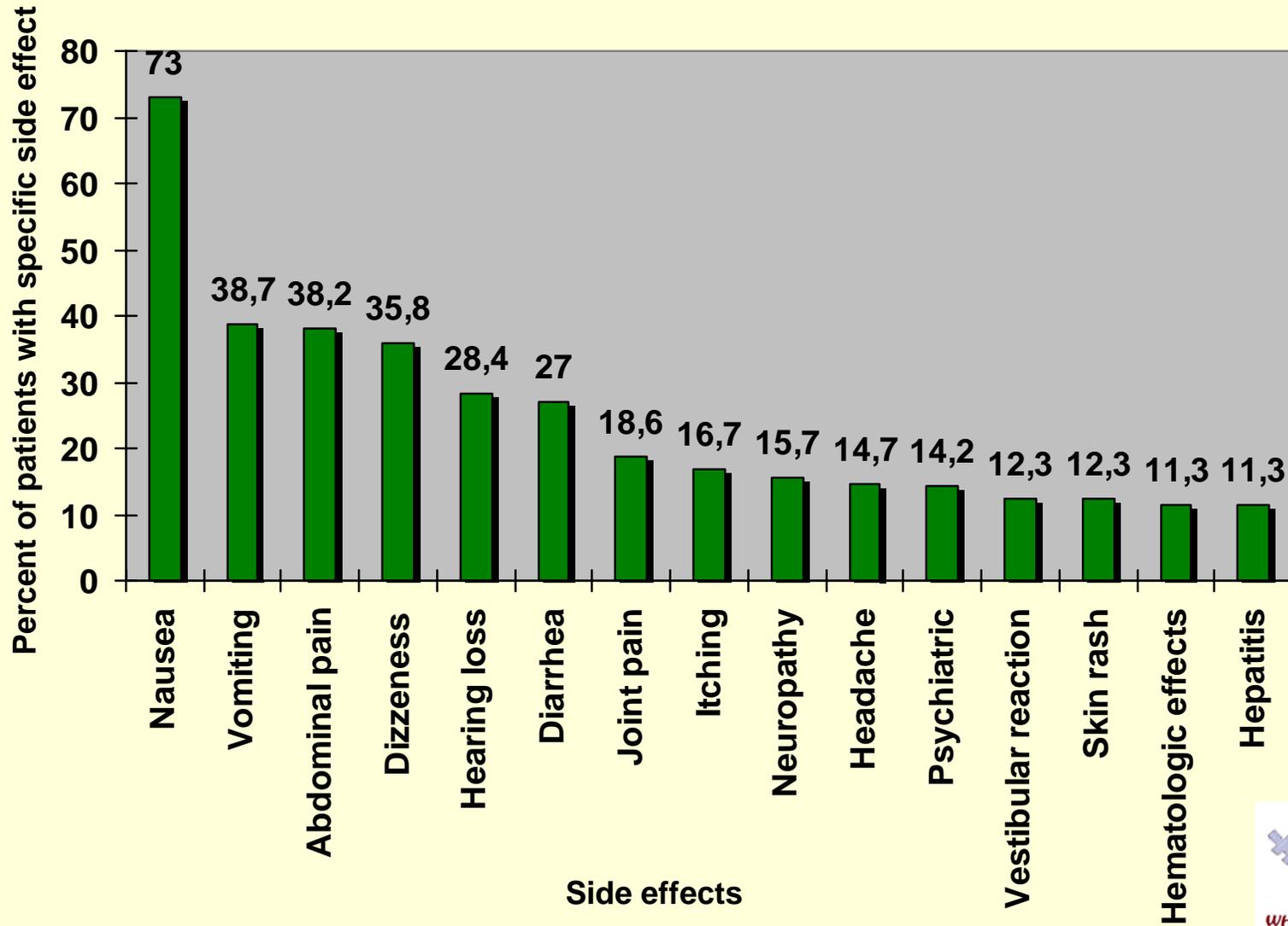
Prophylaxis of neurological complications of cycloserine	Vitamine B6
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam, clonazepam
Insomnia	Dimenhydrinate
Psychosis	Haloperidol, thiorazine, risperidone
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Peripheral neuropathy	Pyridoxine (vitamin B6) Amitriptyline, Meclizine, dimenhydrinate, prochlorperazine, promethazine
Vestibular symptoms	
Musculoskeletal pain, arthralgia, headache	Ibuprofen, paracetamol, codeine

Frequency of adverse reactions associated with second line drugs

Adverse events - results from 5 DOTS-Plus projects

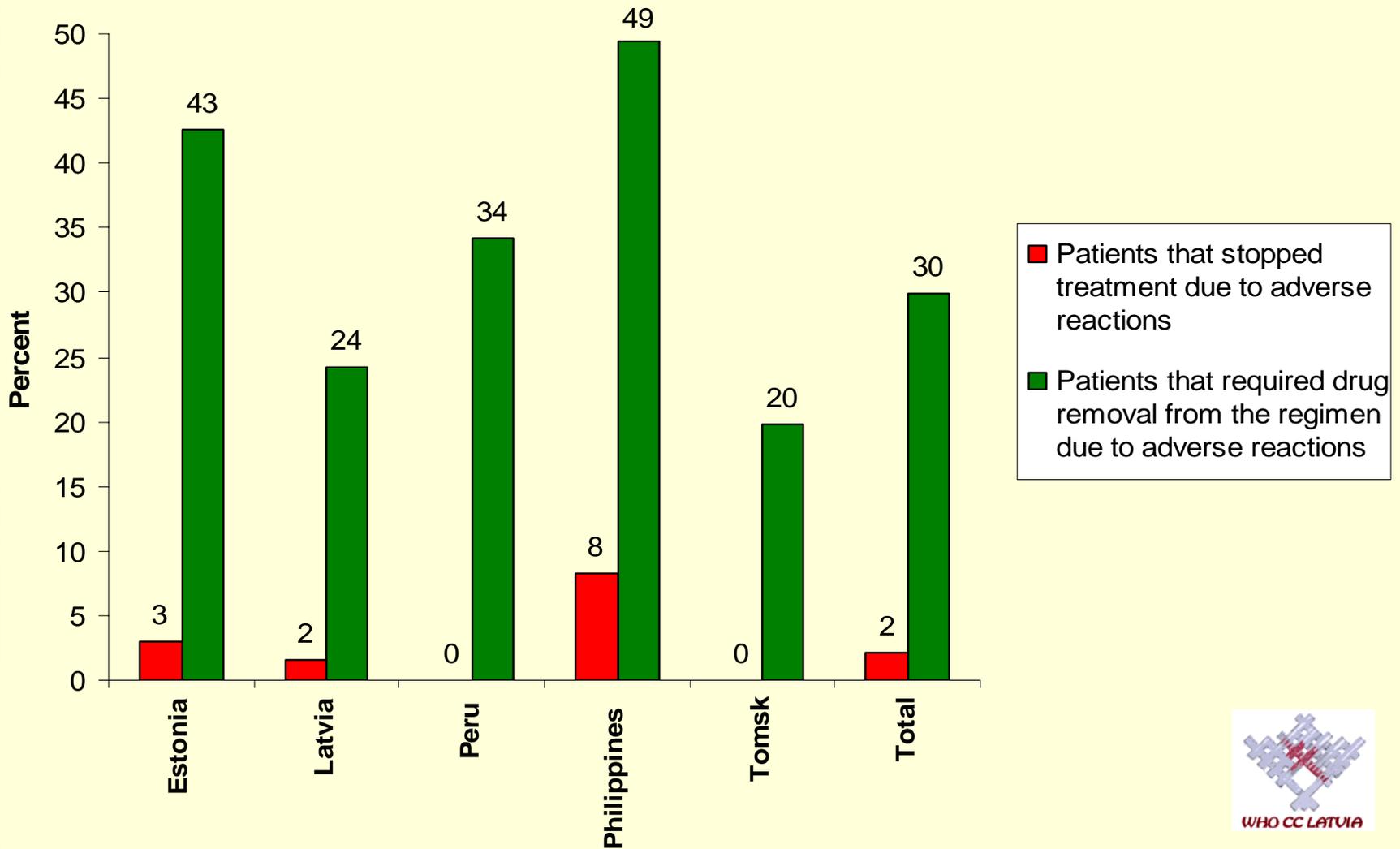
- Only 2% of patients stopped treatment but 30% required removal of the suspected drug(s) from the regimen due to adverse events
- The five most common adverse events were
 - *nausea/vomiting* (32.8%)
 - *diarrhoea* (21.1%)
 - *arthralgia* (16.4%)
 - *dizziness/vertigo* (14.3%),
 - *hearing disturbances* (12.0%)

Frequency of Specific Side Effects Cohort 2000, Latvia

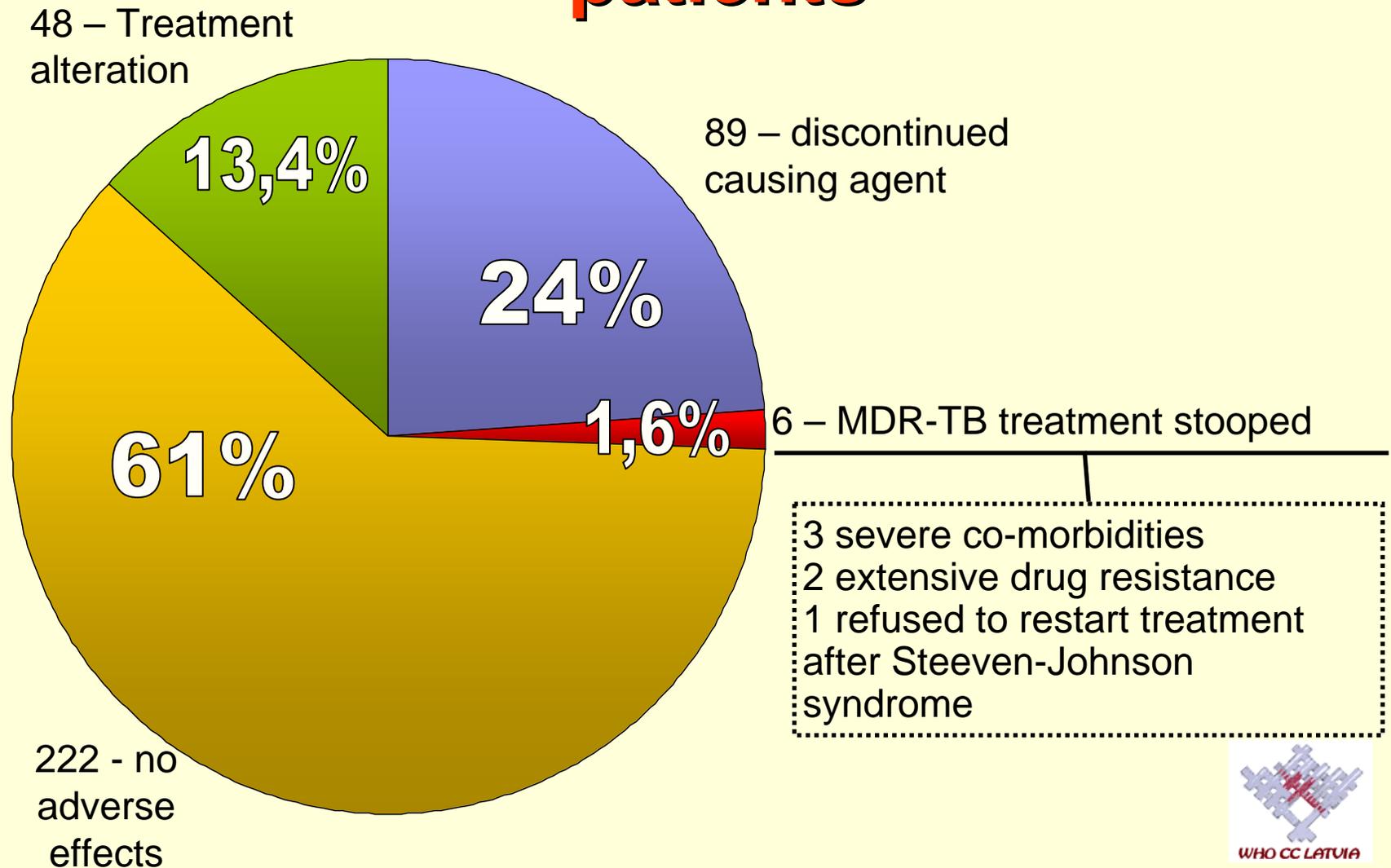


Adverse events 5 DOTS-Plus projects

Treatment continuity in patients enrolled on MDR-TB treatment



Management of adverse effects on MDR-TB treatment regimen for 367 patients

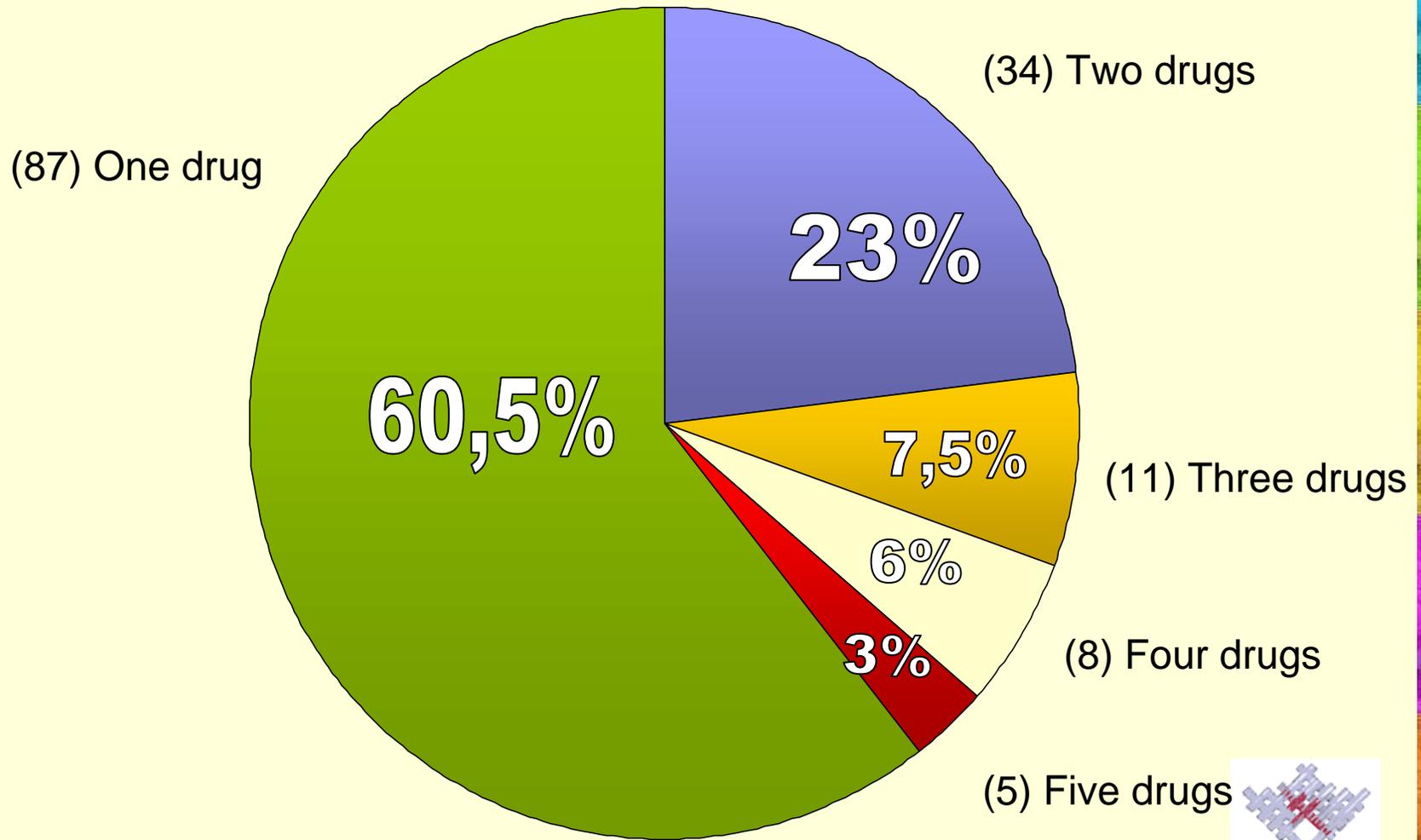


Patients with Drug Permanently Stopped

Year 2000, N = 204 patients

	Month 1-6	Month 7-12	Month 13-18	Total # Over Course of Therapy	Total Patient s Using Drug	Total % of All Persons on Drug
PAS	21	12	1	35	125	28%
Prothionamide	20	12	6	36	187	19%
Kanamycin	18	7	2	26	136	19%
Thiacetazone	13	6	6	25	180	14%
Capreomycin	4	5	2	11	123	9%
Pyrazinamide	8	5	1	13	149	9%
Cycloserine	6	5	1	12	171	7%

Number of drugs causing adverse effects for one patient (total 145 patients)



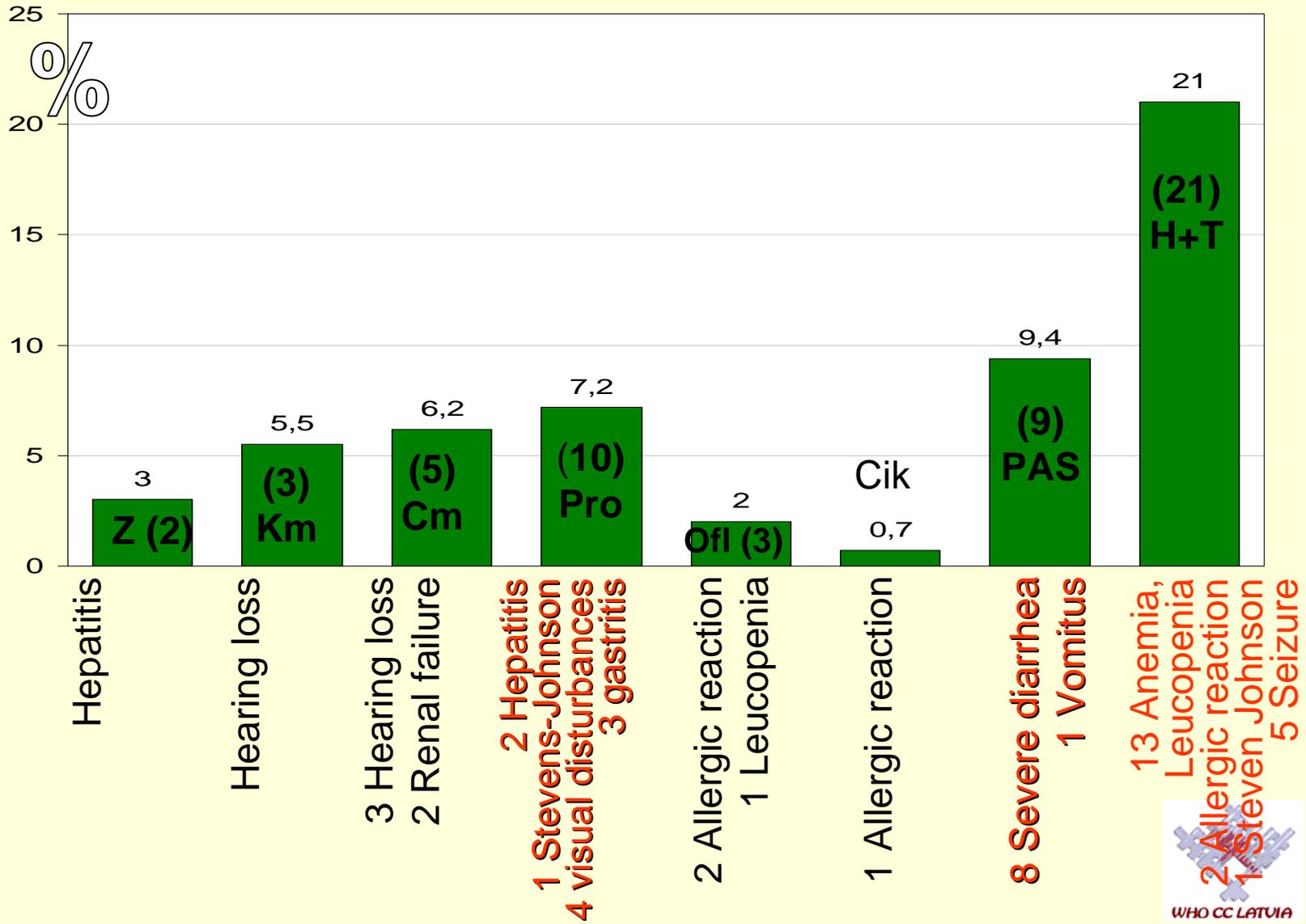
Mean interval from initiation of Tx to occurrence of adverse effects

Adverse effect	Patients n (%)	Mean interval from initiation of Tx to occurrence of adverse event (months)
Mild gastritis	60 (100)	Not available
Dermatological effects	26 (43,3)	Not available
Peripheral NS	12 (20)	9,0
Depression	11 (18,3)	9,1
Anxiety	7 (11,7)	8,5
Hypothyroidism	6 (10)	10,8
Psychotic symptoms	6 (10)	3

Mean interval from initiation of Tx to occurrence of adverse effect

Adverse effects	Patients n (%)	Mean interval from initiation of Tx to occurrence of adverse effect, months
CNS	5 (8,3)	6,4
Arthralgias/arthritis	4 (6,7)	7,8
Hearing loss	4 (6,7)	13,8
Renal toxicity	2 (3,3)	14,5
Hepatitis	1 (1,7)	3
Severe gastritis	1 (1,7)	1

Adverse events by causing drug for 152 (85 adverse events) MDR-TB patients



Conclusions

- ❖ Management of adverse effects is important part of DOTS Plus program it includes:
 - ❖ Training and education
 - ❖ Monitoring and registration of side effects
 - ❖ Proper management if side effects occurs
 - ❖ Psychosocial support for patients
 - ❖ Ancillary drugs