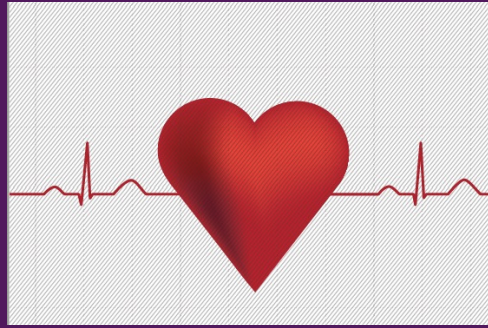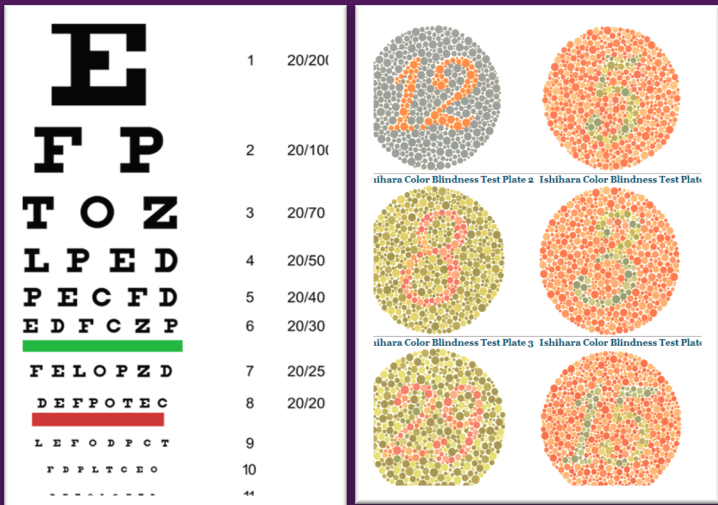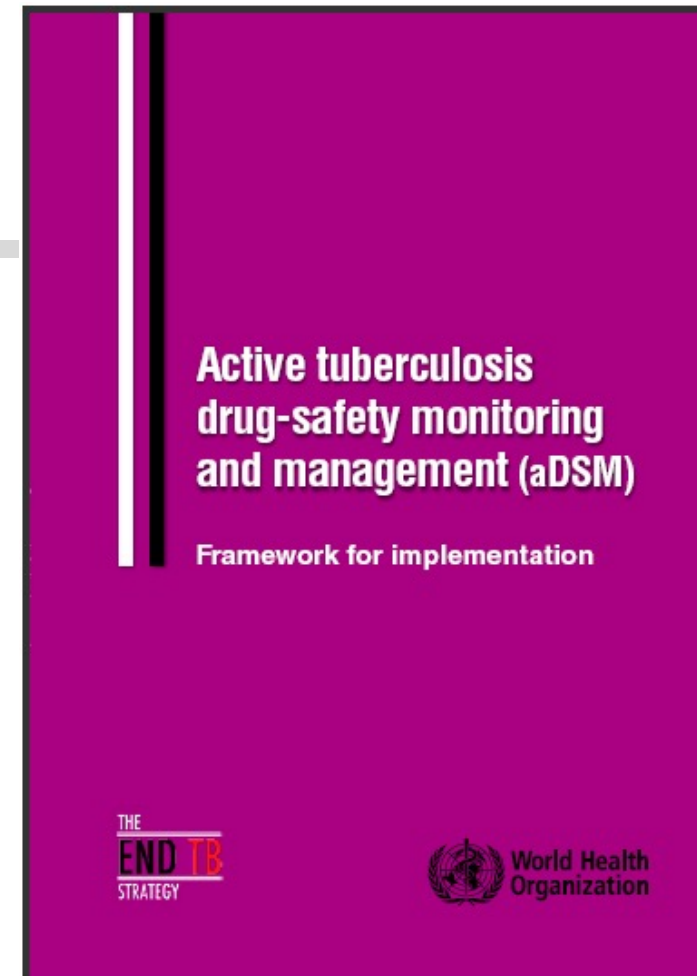# aDSM application: Clinical monitoring of patients on the BPaL regimen

Training of Trainers for the BPaL Operational Research
Philippines, 19-21 May 2021

Mamel Quelapio, MD
Consultant, KNCV

1

- **Active TB drug-safety monitoring and management (aDSM) :** active and systematic <u>clinical</u> and <u>laboratory</u> assessment of patients on treatment with new TB drugs, new MDR-TB regimens or XDR-TB regimens to <u>detect, manage</u> and <u>report</u> suspected or confirmed drug toxicities

- **Adverse events (AE)**: Any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which **<u>does not</u>** necessarily have a causal relationship with this treatment

- **Adverse drug reactions (ADR)**: a **response*** to a medicine which is noxious and unintended, and which occurs at doses normally used in humans

  * Response: a <u>causal</u> relationship between a medicine and an adverse event is at least a reasonable possibility

Active tuberculosis drug-safety monitoring and management (aDSM)

Framework for implementation

THE END TB STRATEGY

World Health Organization

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2

Adverse Event (AE)

- **AE:**
  - Any symptom / sign / laboratory abnormality that was **not present** when the treatment was initiated or during screening

  - Any **worsening** of a symptom / sign / laboratory abnormality already present when the treatment was initiated (present during screening but got worse)

  - **New or worsening TB symptoms and signs**, even if part of the normal course of TB progression, are considered AEs

BPaL OR objectives

Primary objectives:

To estimate the:

- effectiveness of the BPaL regimen by assessing the end of treatment outcome
- **safety of the BPaL regimen by determining the rates of serious adverse events (SAEs)**

Secondary objectives

To determine the:

- Time to sputum culture conversion
- Recurrence-free cure rates at 6 and 12 months post-treatment completion.
- **Proportion of patients with AEs of special interest (AESIs)**

Reporting of AEs in the BPaL OR

Adverse event types that need reporting (AE Form for BPaL):

1   AE leading to treatment discontinuation or change in drug dosage

2   AE of special interest

3   Serious adverse event (SAE)

1 | **AE** leading to treatment changes

An AE that results to:

1. Dose modification

2. Interruption – temporary

3. Discontinuation - permanent interruption

LIF**T**B

2 **AE of special interest (AESI):**

an AE that occurred during clinical trials and for which the monitoring programme is specifically sensitized to report regardless of its seriousness, severity or causal relationship to the TB treatment.

AESIs in the BPaL OR:
1. Peripheral neuropathy
2. Myelosuppression – anemia (low hemoglobin), thrombocytopenia (low platelets), neutropenia (low neutrophils)
3. Optic neuritis
4. Hepatotoxicity
5. QT prolongation

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3 **Serious adverse event (SAE):** an AE that leads to:

death or a life-threatening experience

hospitalization or prolongation of hospitalization

persistent or significant disability; or

a congenital anomaly

does not immediately result in one of the above outcomes but requires an intervention to prevent it from happening

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Grading the severity of a sign or symptom: SEVERITY GRADING SCALE

Look for the sign or symptom and assess the severity:

- e.g., Patient has ALT increase at 100 U/L (normal <40)

Condition term	Grade 1	Grade 2	Grade 3	Grade 4
Alanine Aminotransferase (ALT or SGPT) Increased	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN

- e.g. Patient presents vomiting continuously for 2 days, he is dehydrated and has to be hospitalized.

Condition term	Grade 1	Grade 2	Grade 3	Grade 4
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	Physiologic consequences requiring hospitalization or requiring parenteral nutrition

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**Evaluation schedule: Baseline, during and post-treatment**

	Baseline	2 weeks	Monthly	End of treatment	6- and 12-months after treatment completion
A — CLINICAL EVALUATION					
Clinical assessment*[1]	X	X	X	X	X
Psychosocial assessment*[2]	X	X	X	X	X
Performance status[3]	X				
Weight / BMI	X	X	X	X	X
Peripheral neuropathy screen[4]	X	X	X	X	X
Chest X-Ray	X		X-If no response to treatment	X	X
ECG	X	X	X	X	X-If indicated
Visual acuity and colour discrimination screen	X	X	X	X	X
Assessment and follow-up of AEs	X(X)	X(X)	X(X)	X(X)	X(X)
Treatment outcome assessment				X	X
B — BACTERIOLOGIC EVALUATION					
Gene Xpert	X				
Sputum smear	X		X	X	X
Sputum culture[5]	X(X)		X (X)	X(X)	X(X)
Sputum drug susceptibility testing [6]	X (X)		X-If culture positive[7]		
Other sample smear	X		X-If no response to treatment		
Other sample culture	X(X)		X-If no response to treatment		
Other sample drug susceptibility testing	X		X-If culture positive[7]		
C — LABORATORY EVALUATION					
Full blood count	X	X	X	X	X-if indicated
Liver function tests (AST, ALT, bilirubin)	X	X	X	X	X-if indicated
Thyroid stimulating hormone (TSH)	X		X - if indicated		
Serum electrolytes (Na, K, Ca, Mg)	X		X	X	X-if indicated
Serum amylase			X - if indicated		
Kidney function tests (Urea, Creatinine)	X		X - if indicated		
BSL (fasting or random)[8]	X				
HIV / HBV / HCV tests	X				
Pregnancy test[9]	X		X - if indicated		

Evaluations for patients enrolled on BPaL

| A | Clinical evaluation |

| B | Bacteriologic evaluation |

| C | Laboratory evaluation |
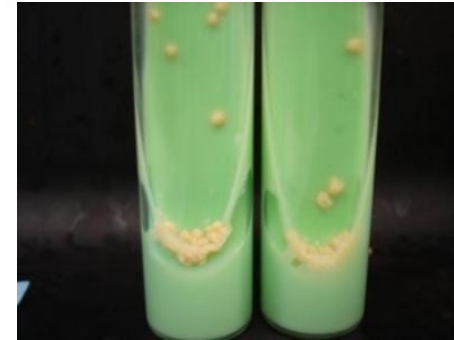
A Clinical evaluation

	Baseline	2 weeks	Monthly	End of treatment	6- & 12-months post-treatment
Clinical assessment*[1]	X	X	X	X	X
Psychosocial assessment*[2]	X	X	X	X	X
Performance status[3]	X				
Weight / BMI	X	X	X	X	X
Peripheral neuropathy screen[4]	X	X	X	X	X
Chest X-Ray	X		X-If no response	X	X
ECG	X	X	X	X	X-If indicated
Visual acuity and colour discrimination screen	X	X	X	X	X
Assessment and follow-up of AEs	X(X)	X(X)	X(X)	X(X)	X(X)
Treatment outcome assessment				X	X

- **Clinical assessment ***
  - [*1] Vital signs, TB symptom screen, pain, nausea, appetite and nutrition, diarrhea, candidiasis, mental status assessment. Clinical assessment should focus on a) monitoring response to treatment and b) addressing common symptoms associated with TB treatment and long-term antibiotic use (ex candidiasis), with the goal of supporting adherence.

- **Psychosocial assessment ***
  - [*2] Food security, housing, mental state, substance use. Psychosocial assessment should offer an opportunity to assess supportive factors for treatment adherence and should be directly linked to relevant interventions wherever possible per country-specific questionnaires

- **Performance status**
  - [3] Assessed by Karnofsky Performance Status Scale

* Guidance for physicians; no standardized data collection is required.

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The Karnofsky Performance Scale Index allows patients to be classified by their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

Karnofsky Performance Status Scale

Definitions Rating (%) Criteria		
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance
	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

Body Mass Index (BMI)

$$\boxed{\text{BMI} = \text{kg/m}^2}$$

where   kg is a person's weight in kilograms

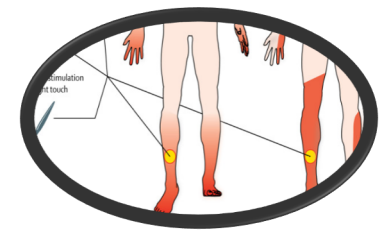 m^2 is their height in metres squared

A **BMI:**

     $\geq$ 25.0   = **overweight**

     18.5 to 24.9   = **healthy**

Brief Peripheral Neuropathy Screen (BPNS)

Grading of subjective symptoms: Patient to rate the severity of each symptom on a scale from 01 (mild) to 10 (most severe) for R and L feet/legs. Enter the score for each symptom, R and L.

Normal	Mild ---Severe									
00	01	02	03	04	05	06	07	07	09	10

Use the single highest severity score above to obtain a subjective sensory neuropathy score

Symptoms	Right	Left
a. Pain, aching, or burning in feet, legs		
b. "Pins and needles" in feet, legs present for at least 2 weeks		
c. Numbness (lack of feeling) in feet, legs present for at least 2 weeks		

Subjective Sensory Neuropathy Score	Severity grade
00	0
01 – 03	1
04 – 06	2
07 – 10	3
Life-threatening	4
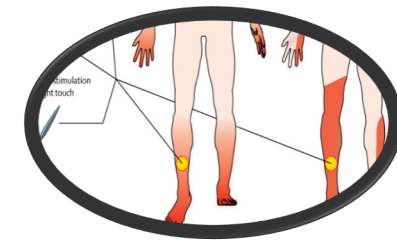
BPNS (Scoring and severity grading)

Normal	Mild --Severe									
00	01	02	03	04	05	06	07	07	09	10

Symptoms Subjective sensory neuropathy score ➡	Right	Left
a. Pain, aching, or burning in feet, legs	0	0
b. "Pins and needles" in feet, legs present for at least 2 weeks	3	4
c. Numbness (lack of feeling) in feet, legs present for at least 2 weeks	0	0

Severity Grade	Grade 1	Grade 2	Grade 3	Grade 4
Neurosensory alteration	Mild discomfort; no treatment required; and/or **BPNS subjective sensory neuropathy score 1-3 on any side.**	Moderate discomfort; non-narcotic analgesia required; and/or **BPNS subjective sensory neuropathy score 4-6 on any side.**	Severe discomfort; or narcotic analgesia required with symptomatic improvement; and/or **BPNS subjective sensory neuropathy score 7-10 on any side.**	Incapacitating; or not responsive to narcotic analgesia

Peripheral neuropathy: narcotic and non-narcotic analgesics

Non-narcotic analgesics: weaker non-prescription drugs generally given for headaches, muscular aches and pains of inflammatory origin.
Examples:
- Aspirin, acetaminophen (no anti-inflammatory effect)
- Nonsteroidal anti-inflammatory drugs (NSAIDs), e.g., ibuprofen, naproxen, or prescription Cox-2 inhibitors (e.g., Celebrex)

**Narcotic (or opioid) analgesics or opiates**: strong drugs for moderate to severe pain that induce tolerance and drug dependence,
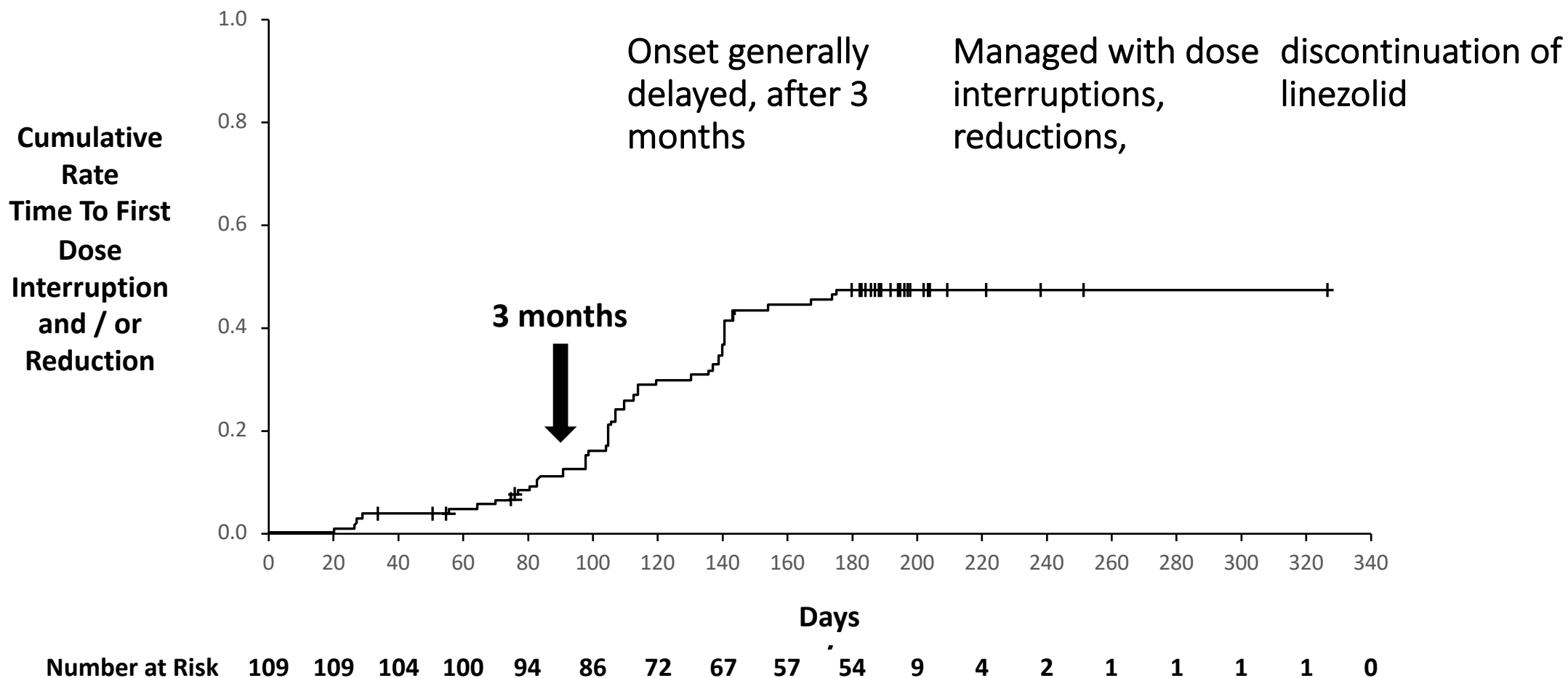Examples:
- Morphine
- Synthetic narcotic drugs, such as methadone
- Tramadol
- Oxycdon
- Fentanyl

Anticonvulsants used to treat neuropathic pain; have the tendency for abuse and are prescription agents:
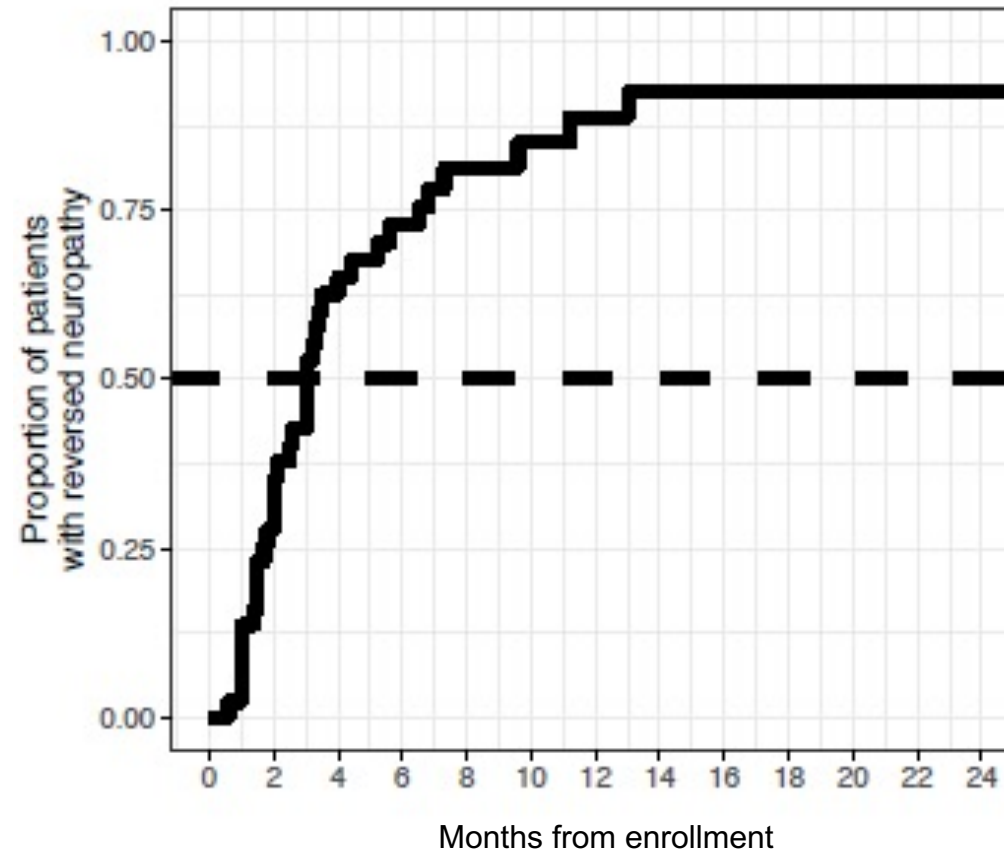- Gabapentin (Neurontin®)
- Pregabalin (Lyrics ®)

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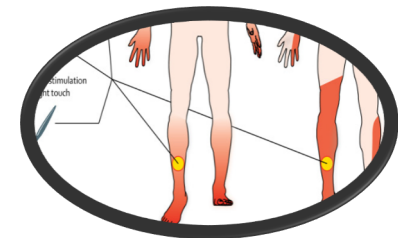
Peripheral neuropathy: delayed onset, managed with dose modifications

Time-course for Improvement in **Peripheral Neuropathy**

Time from first visit when a mean score is moderate-severe (N=45)
to improvement to none or mild score

Score is the mean of scores of
0-10 for each of 4 questions on the Brief Peripheral Neuropathy Rating Scale. Mild is a mean score ≤ 2; Mod-severe is a mean score>2

Months from enrollment
Based on symptom rating in the Brief Peripheral Neuropathy Rating Scale. *Note that follow up is ongoing*

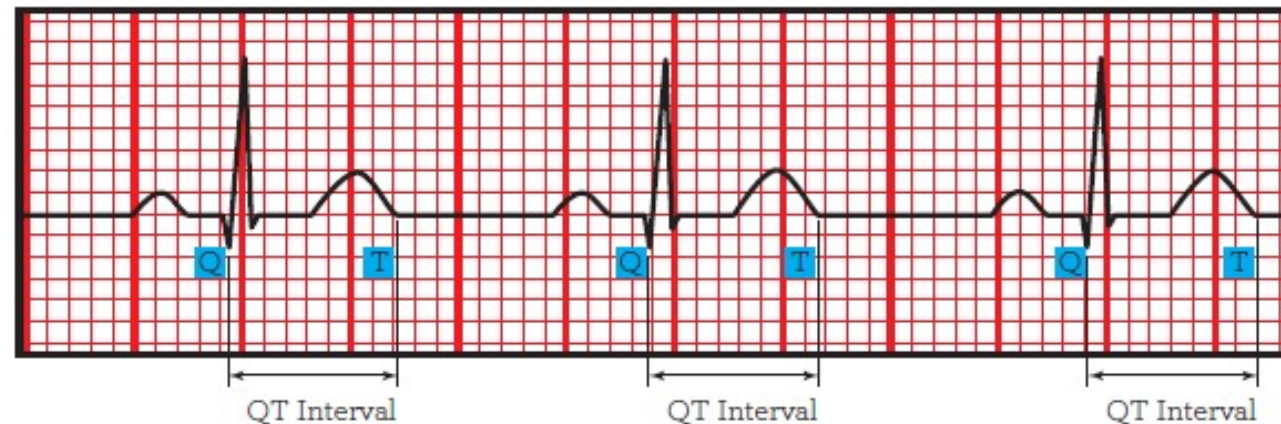*Presented at 2020 CROI, Savic et al.*

ECG – QTcF calculation
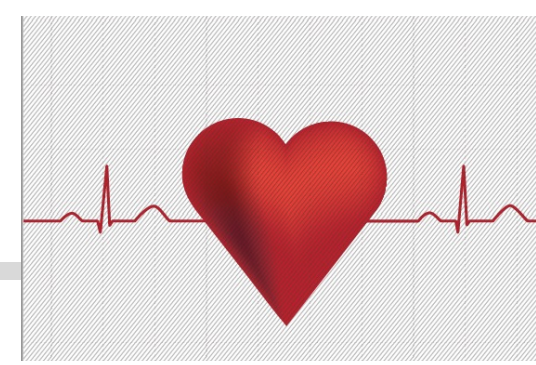
Steps:

From the ECG tracing: Speed is preferably 25mm/sec

1. Choose 3 successive heartbeats from Lead II, V5 or V6.
2. Manually measure the QT intervals. Choose the beat with maximum QT interval.

QT Interval   QT Interval   QT Interval

3. Measure the RR interval or HH (60/RR in sec)
4. Get the QTcF value.

$$QT_{cF} = \frac{QT}{\sqrt[3]{RR}}$$

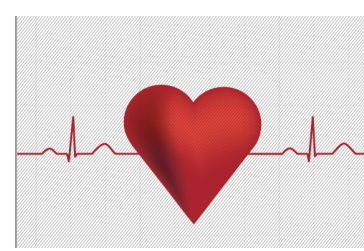**Options for calculating the QTcF value**

1. Mobile app (QxMD, etc.)

    Calculate (Medical Calculator) by Q...
    QxMD Medical Software›
    OPEN

2. Website: https://www.medcalc.org/clinicalc/corrected-qt-interval-qtc.php

3. QTcF Nomogram

4. Manual calculator

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Severity grading scale of QTcF prolongation

| Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Prolongation of QTcF	QTcF 450 – 480 ms.	QTcF interval 481 – 500 ms.	QTcF >= 501 ms without signs/symptoms of serious arrhythmi.	QTcF >= 501 or >60 ms change from baseline and one of the following: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia.

Optic neuritis

- Inflammation of the optic nerve that can result to permanent vision loss

- Visual tests: baseline and monthly, ad hoc
  - VA: Snellen Eye Chart (and E chart)
  - Color vision/blindness test: Ishihara chart

- VA change from baseline, do formal red/green color testing asap and a fundoscopic exam of the bilateral optic nerves.

Optic neuritis
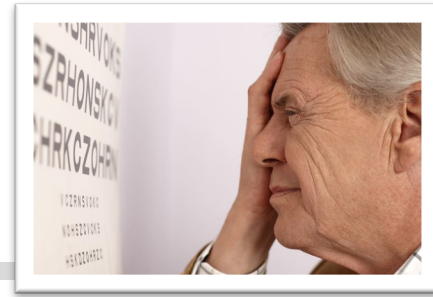
- Signs and symptoms:

  - Painless (underscores need for VA testing), progressive, bilateral, symmetrical **visual decline** (20/40-20/200 or 6/12 – 6/60) which can extend to total blindness

  - Decreased **visual acuity** (VA) and changes in **color perception** (red/green: first sign) "Dyschromatopsia" (red is less bright) or generalized loss of color perception

  - Loss of visual acuity may start with a **blur** at the point of fixation (a relative scotoma) or an area of depressed vision and interferes with central vision)

  - **Pain in moving the eye**

- In Nix, there were 2 patients with optic neuritis (4.5-5 months of treatment) that completely reversed with discontinuation of Lzd
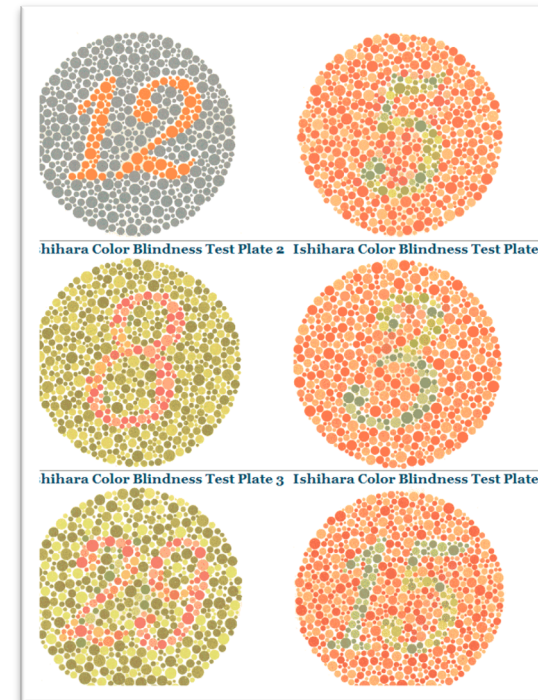
Visual tests
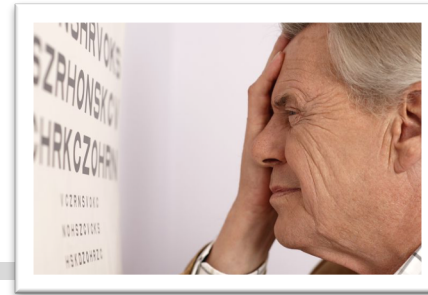
- **Visual acuity**
  - Snellen Chart

- **Color vision screen**
  - Ishihara plates

Visual acuity
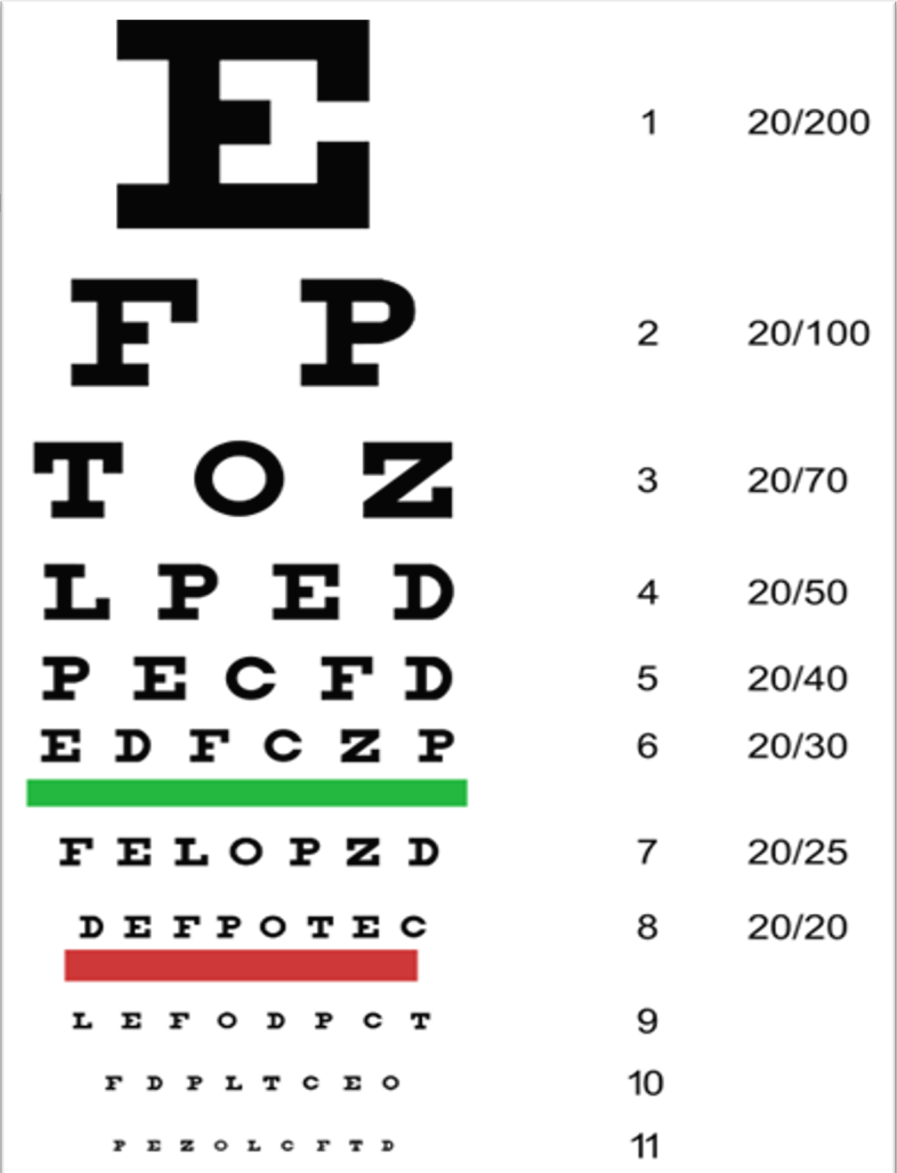
Snellen Chart

- Measures sharpness of central vision

- Chart is standardized for size and contrast

- DO NOT PHOTOCOPY

- 11 rows of capital letters.

- 20 feet away (or 6 meters)

Normal vision = 20/20 (ft) (or 6/6 in m)

1	20/200
2	20/100
3	20/70
4	20/50
5	20/40
6	20/30
7	20/25
8	20/20
9	
10	
11	

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Snellen Chart for Visual Acuity

- Distance spectacles may be worn; record with spectacles on. All future vision tests done with spectacles on.

- Test each eye separately, the "bad" eye first.

- To score, refer to the number on the right, e.g., 20/200 up to 20/20 (feet).* The smallest line he can read (the VA) will be expressed as a fraction:
  - Upper number = distance the chart is from the patient (20 feet)
  - Lower number = distance at which a person with no impairment should be able to see the chart

*Metric: 6/6 up to 6/60 meters
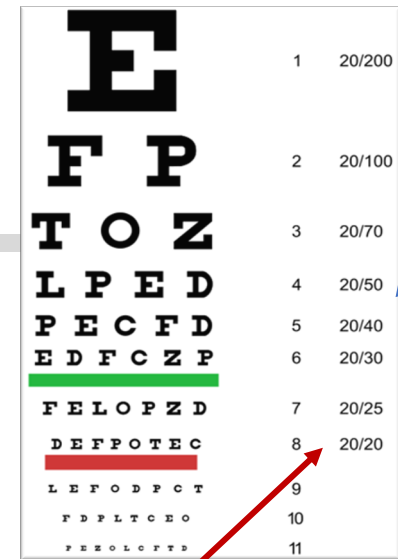
Example:

Right VA = 20/20 with correction	Left VA = 20/50 with correction
Able to read up to the 8th line with glasses on.	Able to read up to the 4th line only with glasses on. *An average person could read this at 50 feet away.*

Optic Neuritis

Severity Grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Optic nerve disorder	Asymptomatic or mild symptoms; clinical or diagnostic observations only or **unable to read 4 or more plates in color vision test**	Symptomatic; **moderate decrease in visual acuity (20/40 [6/12] or better) or drop of 2 lines on VA (Snellen) chart or unable to read 4 or more plates in color vision test.**	Limiting vision in the affected eye; **visual acuity worse than 20/40 [6/12] but better than 20/200 [6/60]) or drop of more than 2 lines (Snellen chart) or unable to read 4 or more plate (color vision test)**	**Blindness (20/200 [6/60] or worse) in the affected eye.**

Snellen Chart for Visual Acuity

If unable to read the biggest letter at 20 feet, move 1-3 feet closer.

If able to read the biggest letter only at 3 feet away, **VA=3/200**.

If unable to read biggest letter even at 3 feet:

- hold your fingers up and see if he can count them

  VA = Counting fingers (CF)

- If not, wave your hand

  VA = Hand movement (HM)

- If not, shine a flashlight toward his eye in 4 directions/quadrants

  VA = Light perception (PL) on right/left upper/lower quadrant
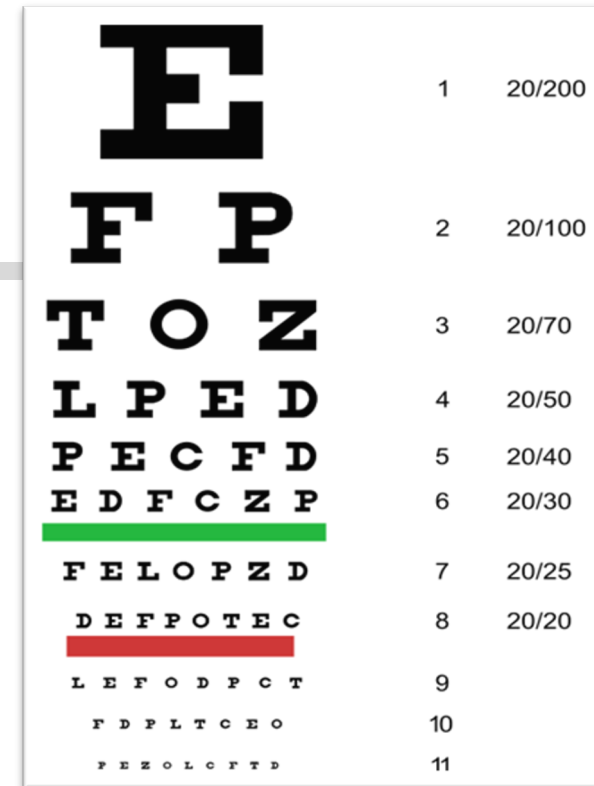
Example:

Right VA=	NPL or X	NPL or X	Left VA =	CF
	NPL or X	NPL or X		
Right eye no perception of light on all 4 quadrants at 3 feet away			Able to count your fingers at 3 feet away	

NPL – no light perception

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Color vision test

Ishihara plates

- Color scales are important;
- DO NOT PHOTOCOPY
- 11 plates (Full =38 plates)
- 75 cm away, circles at eye level
- Within 3 (-5) seconds

No. of correctly read plates	Vision
10 plates	**Normal**
8-9 plates	Further testing if patient truly has red/green deficiencies
≤7 plates	Abnormal

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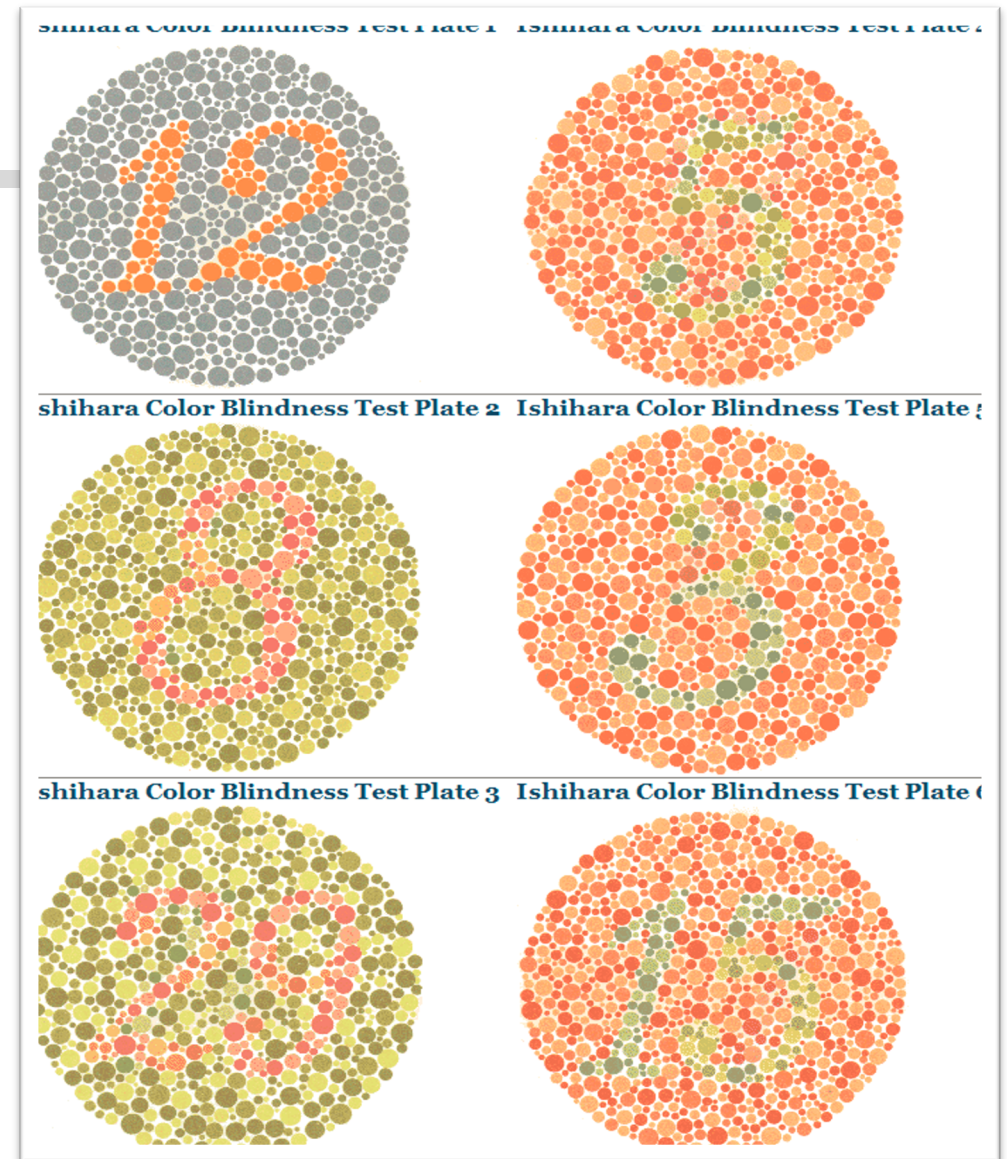
c Laboratory evaluation

	Baseline	2 weeks	Monthly	End of treatment	6- & 12- months post-treatment
Full blood count	X	X	X	X	X-if indicated
Liver function tests (AST, ALT, bilirubin)	X	X	X	X	X-if indicated
Thyroid stimulating hormone (TSH)	X		X - if indicated		
Serum electrolytes (Na, K, Ca, Mg)	X		X	X	X-if indicated
Serum amylase			X - if indicated		
Kidney function tests (Urea, Creatinine)	X		X - if indicated		
BSL (fasting or random)[8]	X				
HIV / HBV / HCV tests	X				
Pregnancy test[9]	X		X - if indicated		

- **Full blood count:**
  - Hemoglobin for anemia
  - Neutrophils or segmenters for neutropenia
  - Platelets for thrombocytopenia

Severity grading scale of **myelosuppression**

Severity Grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Hemoglobin	10.5 - 9.5 g/dL	9.4 – 8.0 g/dL	7.9 – 6.5 g/dL	< 6.5 g/dL
Platelets	99,999-75,000/mm³	74,999-50,000/mm³	49,999-20,000/mm³	< 20,000/mm³
While blood cells	<LLN - 3,000/mm³	<3,000 - 2,000/mm³	<2,000 - 1,000/mm³	< 1,000 /mm³
Absolute neutrophil count	1500 - 1000/mm³	999 - 750/mm³	749 - 500/mm³	<500/mm³

EndTB Severity Grading Scale for Adverse Events, version 5.0.
Available from: http://endtb.org/resources/pharmacovigilance

Anemia
Hemoglobin

Age/ Sex : 59 Y M
Date of Birth : 1960-11-04
Location/ Ward : OPD
Requesting Physician : ,

Hospital No. : 1079911
Date/Time Requested : Jun 03, 2020 10:40 AM
Date/Time Received : Jun 17, 2020 11:21 AM
Date/Time Reported : Jun 17, 2020 11:55 AM

HEMATOLOGY AND COAGULATION

EXAMINATION		RESULT	UNITS	REFERENCE
COMPLETE BLOOD COUNT				
Red Blood Cell	L	2.7	10^12/L	4.7-6.2
Hemoglobin	L	98	g/L	130 - 160
Hematocrit	LO	0.26	volume %	0.37 - 0.49
MCV		94.2		78 - 98
MCHC	H	38.0	g/dL	33.0-36.0
MCH	H	35.8	pg	28.0-33.0
RDW	H	16.2	%	11 - 14
White Blood Cell	L	4.0	10^9/L	5.0 - 10.0
DIFFERENTIAL COUNT				
Neutrophils		50	%	40-70
Lymphocyte		26	%	20-45
Monocyte		5	%	0-10
Eosinophil	H	18	%	0-10
Basophil		1	%	0-1
Platelet Count	L	96	10^3/uL	150 - 350
MPV		12	fL	8 - 12

Severity Grading Scale of anemia in g/dL

Hemoglobin

Grade 1	Grade 2	Grade 3	Grade 4
10.5-9.5 g/dL	9.4-8.0 g/dL	7.9-6.5 g/dL	<6.5 g/dL

Result of Hg is in g/L; hence, convert to g/dL

Convert g/L to g/dL by dividing by 10

Result	Converted result
98 g/L divided by 10 →	9.8 g/dL

Neutropenia
Absolute neutrophil count (ANC)

Severity Grading Scale of neutropenia (ANC) in x 10^3 /uL or /mm³			
Neutrophils			
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
1500-1000/mm^3	999-750/mm^3	749-500/mm^3	<500/mm^3

Result of WBC is in x 10^9 /L ; hence, convert to /mm³

Convert x10^9 /L to /mm³ by multiplying with 1000	
Given result	Converted result
4.0 x 10^9 /L X 1000 ➡	4000/mm³

Calculate ANC:

WBC X neutrophils

4000/mm³ X 50% = 2000/mm³

Within normal limits

HEMATOLOGY AND COAGULATION

Age/ Sex : 59 Y M
Date of Birth : 1960-11-04
Location/ Ward : OPD
Requesting Physician : ,

Hospital No. : 1079911
Date/Time Requested : Jun 03, 2020 10:40 AM
Date/Time Received : Jun 17, 2020 11:21 AM
Date/Time Reported : Jun 17, 2020 11:55 AM

EXAMINATION		RESULT	UNITS	REFERENCE
COMPLETE BLOOD COUNT				
Red Blood Cell	L	2.7	10^12/L	4.7-6.2
Hemoglobin	L	98	g/L	130 - 160
Hematocrit	LO	0.26	volume %	0.37 - 0.49
MCV		94.2		78 - 98
MCHC	H	38.0	g/dL	33.0-36.0
MCH	H	35.8	pg	28.0-33.0
RDW	H	16.2	%	11 - 14
White Blood Cell	L	4.0	10^9/L	5.0 - 10.0
DIFFERENTIAL COUNT				
Neutrophils		50	%	40-70
Lymphocyte		26	%	20-45
Monocyte		5	%	0-10
Eosinophil	H	18	%	0-10
Basophil		1	%	0-1
Platelet Count	L	96	10^3/uL	150 - 350
MPV		12	fL	8 - 12

Example:

WBC count	2.6 x 10^9/L
Neutrophils	52%
Lymphocyte	27%
Monocyte	5%
Eosinophils	5%

Calculate ANC:

WBC X neutrophils

= 2.6 x 10^9/L   X 1000 =2,600/mm^3

=2600/mm^3 X 52% = 1352/mm^3

Severity Grading Scale of neutropenia (ANC) in 10^3 /uL			
Absolute neutrophil count (ANC)			
Grade 1	Grade 2	Grade 3	Grade 4
1500-1000/mm^3	999-750/mm^3	749-500/mm^3	<500/mm^3

Thrombocytopenia
Platelets

HEMATOLOGY AND COAGULATION

Age/ Sex : 59 Y M
Date of Birth : 1960-11-04
Location/ Ward : OPD
Requesting Physician :,

Hospital No. : 1079911
Date/Time Requested : Jun 03, 2020 10:40 AM
Date/Time Received : Jun 17, 2020 11:21 AM
Date/Time Reported : Jun 17, 2020 11:55 AM

EXAMINATION		RESULT	UNITS	REFERENCE
COMPLETE BLOOD COUNT				
Red Blood Cell	L	2.7	10^12/L	4.7-6.2
Hemoglobin	L	98	g/L	130 - 160
Hematocrit	LO	0.26	volume %	0.37 - 0.49
MCV		94.2		78 - 98
MCHC	H	38.0	g/dL	33.0-36.0
MCH	H	35.8	pg	28.0-33.0
RDW	H	16.2	%	11 - 14
White Blood Cell	L	4.0	10^9/L	5.0 - 10.0
DIFFERENTIAL COUNT				
Neutrophils		50	%	40-70
Lymphocyte		26	%	20-45
Monocyte		5	%	0-10
Eosinophil	H	18	%	0-10
Basophil		1	%	0-1
Platelet Count	L	96	10^3/uL	150 - 350
MPV		12	fL	8 - 12

Severity Grading Scale of thrombocytopenia = platelets/mm^3

Platelets			
Grade 1	Grade 2	Grade 3	Grade 4
99,999-75,000/mm^3	74,999-50,000/mm^3	49,999-20,000/mm^3	<20,000/mm^3

Result is in x 10^3/uL; hence, convert to /mm^3

Convert 10^3/uL to /mm^3 by multiplying by 1,000

Result	Converted result
96 x 10^3/uL X 1000	96,000 /mm^3
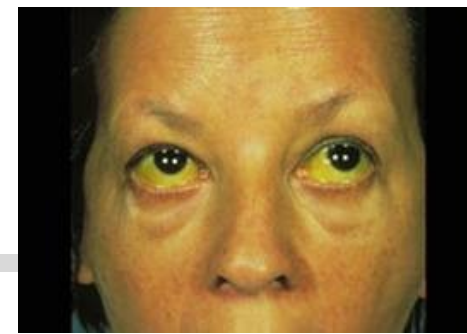
- **Liver function tests:**
  - ALT (SGPT)
  - AST (SGOT)
  - Bilirubin

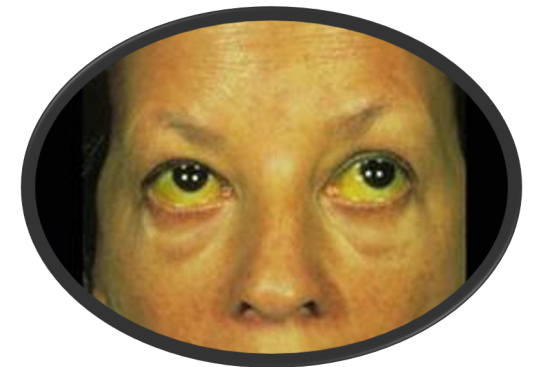|	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
ALT/AST	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Bilirubin	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN

Age : 51Y   Gender : MALE   Room No : OP
Date of Birth : 15-FEB-1964   Date Requested : 08-MAY-2015 12:17 PM
Requesting Doctor :   Date Reported : 08-MAY-2015 01:43 PM

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Test Name	S.I. Units Result	Reference Range	Conventional Units Result	Reference Range
SGOT (AST)	H 36.00 U/L	5.00 - 34.00	36.00 U/L	5.00 - 34.00
SGPT (ALT)	H 58.00 U/L	0.00 - 55.00	58.00 U/L	0.00 - 55.00
Alkaline Phosphatase	40.00 U/L	40.00 - 150.00	40.00 U/L	40.00 - 150.00

Severity grading scale of hepatitis or elevated liver enzymes

Severity Grade	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
ALT /AST	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Bilirubin	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN

EndTB Severity Grading Scale for Adverse Events, version 5.0. Available from: http://endtb.org/resources/pharmacovigilance

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- **Amylase:**
  - Hyperamylasemia (increased pancreatic enzyme): a rare AE in BPaL patients in the Nix trial (not determined to be associated with Bdq)
- **Blood sugar level (fasting or random):**
  - If abnormal at baseline, diabetes mellitus should first be ruled out. If a patient is found to have DM, he should be treated and followed up accordingly
- **Pregnancy test**
  - Only for women of reproductive age

- **Kidney function tests**
  - Urea, creatinine
- **Thyroid stimulating hormone (TSH):**
- **Serum electrolytes**
  - Na, K, Ca, Mg
- **Viral tests:**
  - HIV, Hepatitis B (HBsAg), C (Anti-HCV)
- **Pregnancy test**
  - Only for women of reproductive age

Diagnosis of Diabetes mellitus

	Normal	Pre-diabetes	Diabetes	
Fasting blood sugar (8-10 hour fasting)	< 100 mg/dl **OR** <5.6 mmol/L	100-125 mg/dl OR 5.6 to 6.9 mmol/L	≥ 126 mg/dL OR ≥ 7 mmol/L	2X OR Once with HBa1c ≥ 6.5%
HBa1c*	<5.7%	5.7-6.4%	6.5%	2X
Random blood sugar or OGTT **	<140 mg/dl OR <7.8 mmol/L	140-199 mg/dL OR 7.8-11.0 mmol/L	≥200 mg/dl OR ≥11.1 mmol/L	Once

*Glycated hemoglobin: measures the average blood sugar level for the past 2-3 months; the % of blood sugar attached to hemoglobin, the oxygen-carrying protein in red blood cells
**Oral Glucose Tolerance Test: overnight fasting, test sugar level; drink a sugary liquid and then measure blood sugar periodically in the next 2 hours

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https://www.mayoclinic.org/diseases-conditions/diabetes/diagnosis-treatment/drc

Thank you

Funding for LIFT-TB

Leveraging Innovation for Faster Treatment of Tuberculosis