

Is the Adams D-15 colour vision test a sensitive screening tool for ethambutol- and linezolid-induced optic neuropathy? A retrospective case series

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# Part A: Article in publication ready format

## Cover Sheet

### Title

Is the Adams D-15 colour vision test a sensitive screening tool for ethambutol- and linezolid-induced optic neuropathy? A retrospective case series.

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**Conflict of interests** Nil

**Title Page**

Title: Is the Adams D-15 colour vision test a sensitive screening tool for ethambutol- and linezolid-induced optic neuropathy? A retrospective case series

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**Declaration of interests:** Nil

## **Abstract**

**Background:** Ethambutol hydrochloride and linezolid are commonly used anti-tuberculous agents. Both agents can cause potentially blinding toxic optic neuropathy. Currently there is no low-cost, sensitive screening tool to detect early toxicity before permanent vision loss has occurred.

**Purpose:** To evaluate the ability of the Adams D-15 colour vision test to detect early ethambutol- and linezolid-induced optic neuropathy.

**Methods:** This was a retrospective case series of 15 patients who were screened for ethambutol- and linezolid-induced toxic optic neuropathy. At screening and follow-up visits, a detailed clinical history was taken, a standard of care examination performed and a battery of side-room investigations conducted, including: Farnsworth Munsell D15 (FM D15) and Adams D15 colour vision tests, retinal nerve fiber layer optical coherence tomography (RNFL-OCT) and a Humphrey visual field 24-2 (HVF 24-2). According to the results of these tests, the patients were classified into 3 groups: “No toxicity”, “Uncertain toxicity” or “Confirmed toxicity”.

**Results:** Six patients were classified as “No toxicity”, 3 were “Uncertain toxicity” and 6 were classified as “Confirmed toxicity”. The Adams D15 showed a sensitivity of 100% for detecting a toxic optic neuropathy.

**Conclusion:** The Adams D15 is a sensitive screening tool for the detection of early ethambutol- and linezolid-induced optic neuropathy.

## Introduction

Ethambutol hydrochloride is a commonly used first-line anti-tuberculous agent. Although rare, ocular toxicity in the form of ethambutol-induced optic neuropathy (EON) has been well-documented since its first use in the 1960's.<sup>1</sup> Classically described as dose- and duration-dependent, as well as being reversible on discontinuation, true reversibility of EON remains controversial. At the standard World Health Organization (WHO) recommended daily dose of 15mg/kg, the incidence of toxicity is approximately 1%.<sup>1</sup> Linezolid is a core second-line drug used in the treatment of multidrug-resistant tuberculosis. The exact incidence of toxicity in the form of linezolid-induced optic neuropathy (LON) is uncertain, due to its frequency of use increasing only in recent years. Two recent meta-analyses have reported prevalence rates of between 8 and 13.2%.<sup>2</sup> Unlike ethambutol, toxicity has been shown to be predominantly duration dependant. Recovery of visual function is also more substantial.<sup>2,3</sup>

South Africa has one of the highest burdens of tuberculosis (TB) worldwide. In 2019, the estimated incidence was 360 000 per year.<sup>4</sup> Taking these numbers into consideration, 3600 patients will develop a potentially blinding EON annually in South Africa, unless toxicity is detected in a timely fashion. This number runs into hundreds of thousands globally.<sup>5</sup> International guidelines on the prevention and early detection of EON have been published, but opinion is divided regarding the clinical effectiveness of regular vision tests to enable early detection of toxicity.<sup>1,5</sup> It has been recommended that all asymptomatic patients taking ethambutol should receive monthly screening for signs of EON that should include at least visual acuity and Amsler grid testing. However the clinical burden of screening following these recommendations is not manageable in TB endemic, low-resource settings such as South Africa. Although visual evoked potentials (VEP) and optical coherence tomography (OCT) have been proposed to screen for subclinical EON, the validity, reliability, and reproducibility of screening with these modalities has not

been well studied.<sup>5</sup> Currently there is no low-cost and sensitive screening tool for EON and there are no accepted guidelines on the prevention and early detection of LON.<sup>6</sup>

The aims of this study were therefore to evaluate the ability of the low-cost Adams D15 colour vision test to detect early EON and LON, as well as to document the clinical features of patients who were screened for EON and LON at a single South African tertiary referral centre.

## **Materials and methods**

This was a retrospective study of 15 patients screened for EON and LON in the ophthalmology department of Groote Schuur Hospital, a large, tertiary referral centre in Cape Town, South Africa, between March and December 2019. Multi-drug-resistant patients were referred from local TB hospitals. Routine screening for EON and LON using the Adams D-15 colour vision test began in March 2019. All patients who were screened in the eye clinic for EON and LON over the period 01/03/2019 to 31/12/2019 were included in the study. Inclusion criteria were all patients with a confirmed diagnosis of pulmonary or extrapulmonary TB on either ethambutol or linezolid, or both agents. Exclusion criteria were patients with neurological impairment, learning difficulties making them unable to perform the colour vision tests or patients with co-existing ocular pathology.

At the initial screening visit and all follow-up visits, a detailed clinical history was taken and a standard of care examination was performed. This examination included pinhole or best-corrected visual acuity, anterior segment examination with a slitlamp biomicroscope, intraocular pressures with Goldmann applanation tonometry, posterior segment examination with a 90-diopter lens, pupil examination, FM D15 and Adams D15 colour vision tests, RNFL-OCT on the Heidelberg Spectralis HRA optical coherence tomography imaging platform and a HVF 24-2 on the Humphrey Zeiss HFA 740 perimeter.

Colour vision tests were performed under an illuminant C light source. Failure was defined as more than one transposition. Arrangements were classified as protan, deutan, mixed or non-specific depending on the pattern of defect. A 24-2 threshold Humphrey visual field analysis was performed under the following conditions: size III white stimulus, background illumination of 31.5 Abs and the SITA-FAST algorithm. Optical correction was supplied to those patients with significant refractive errors or those in the presbyopic range. Failure was defined as any visual field defect known to be associated with toxic optic neuropathy, especially a central or cecentral scotoma, or if the patient was unable to perform a visual field.

RNFL-OCT scans were taken using the standard "RNFL thickness" protocol of the Heidelberg Spectralis. The peripapillary six sectors and average RNFL thickness was noted for both eyes. Failure was defined as global or diffuse segments of thickening or thinning beyond 2 standard deviations from normal.

Nurses and technicians with ophthalmic training performed the visual acuity, colour vision, RNFL-OCT and HVF 24-2 measurements. Interpreters were used where necessary. All other procedures and data collection were performed by ophthalmology registrars working in the eye clinic. At the conclusion of screening visits, patients were classified into 3 groups: "No toxicity", "Uncertain toxicity" or "Confirmed toxicity". All patients were managed in concert with their primary care physician. Patients assigned to the "No toxicity" group had no signs of toxicity on clinical examination or with side room investigations. Patients assigned to the "Uncertain toxicity" group had a normal examination, except for an isolated, non-specific colour vision defect or a non-specific visual field defect. These patients were followed-up weekly for repeat evaluation at the neuro-ophthalmology subspecialist clinic. Patients assigned to the "Confirmed toxicity" group showed signs on clinical examination, colour vision or side-room investigations suggestive of toxicity. If the patient was on a single agent, this agent was stopped and the patient followed-up 2 months later. If the patient was on both ethambutol and linezolid, the decision to continue

with treatment depended on the severity of toxicity. If, at the initial visit, early toxicity was detected, the ethambutol would be stopped and the patient followed-up weekly in the neuro-ophthalmology subspecialist clinic. If at these follow-up visits the toxicity was shown to be progressive or stationary, the linezolid was also stopped and the patient seen 2 months later. If signs of toxicity had improved, the linezolid would be continued under close monitoring at the neuro-ophthalmology clinic. If, at the initial visit, advanced toxicity was detected, both agents were stopped and the patient followed up 2 months later.

Basic statistical methods were used to calculate the sensitivities and positive predictive values of the various screening tools used in the study.

## **Results**

Thirty-two patients were referred for LON/EON screening. Seven were excluded due to co-existing ocular pathology. A further 10 were excluded because not all baseline investigations were performed at the first visit. Fifteen patients were therefore included in the study. There were 8 men and 7 women with ages ranging from 23 to 62 years (mean 38 years). Of the 15 patients screened, 6 were included in the “No toxicity” group, 6 were included in the “Confirmed toxicity” group and 3 were included in the “Uncertain toxicity” group. Table I summarizes the toxicity groups and treatment regimens of patients who were screened for EON and LON. No patient in the “Confirmed toxicity” group was over the age of 65 years. None of the patients in the “Confirmed toxicity” group had proven renal dysfunction. Six (40%) patients were HIV positive, which included 2 (33%) of the “Confirmed toxicity” group. Table II provides the sensitivities and positive predictive values of the Adams D15, FM D15, HVF 24-2 and the RNFL-OCT tests. Data is presented for each eye separately. Two eyes were excluded from the RNFL-OCT assessments, due to the scans being unreliable. Table III holds the raw data of all the patients in the “Confirmed Toxicity”

group. The Adams D15 showed a sensitivity of 100% in detecting EON/LON. The test was easy for patients to perform and the results could be interpreted with minimal training.

## **Discussion**

Several colour vision tests have been evaluated as screening tools for the detection of early ethambutol toxicity.<sup>1,7,8</sup> The FM D15 colour vision test has been shown not to be as sensitive as the HVF 24-2, or visually evoked potentials in detecting early toxicity.<sup>9</sup> The Lanthony Desaturated test, a very desaturated version of the FM D15, has been shown to be very sensitive in picking up early colour vision abnormalities in patients taking ethambutol<sup>7</sup>. Cruz et al. also showed that the Lanthony desaturated test has a greater sensitivity for the detection of early colour vision abnormalities, when compared to the FM D15, in patients on TB treatment.<sup>7</sup> The drawback of the Lanthony Desaturated test is that patients find it difficult to perform and it has poor repeatability indices.<sup>7,10</sup>

The Adams D15 is currently a non-commercially available colour vision test, which has a colour saturation that falls in between that of the FM D15 and Lanthony Desaturated test. It has the ability to detect early, acquired colour vision defects in glaucoma and glaucoma-suspects, and has good repeatability indices.<sup>11,12</sup> Using this reasoning, we considered the Adams D15 as a screening tool for early EON/LON. The Adams D15 outperformed the FM D15 with a sensitivity of 100% compared to 83%. These findings were similar to those of Adams et al, who showed that the Adams D15 has an increased sensitivity when compared to the FM D15, in the detection of acquired colour vision defects.<sup>11</sup>

The HVF 24-2 has been shown in multiple studies to be sensitive in picking up early EON/LON, as well as being the most specific diagnostic tool used in screening of TON.<sup>1,5,6,7,9</sup> Visual field defects found in EON are central and cecocentral scotomas, peripheral isopter contraction and bitemporal hemianopsia. Central and cecocentral scotomas being the most common of these patterns.<sup>1,5</sup> Of our “Confirmed toxicity” patients, 4 out of 6 (66%) had central or cecocentral scotomas and 2 out of 6 (33%) were unable

to perform visual field testing. The Adams D15 outperformed the HVF24-2, with a sensitivity of 100% compared to 92%. The disadvantages of the HFV 24-2 are that it requires considerably more expensive equipment, the test is much more complex for patients to perform and the result requires specialist training for interpretation.

Chamberlain et al.'s recent review reported the RNFL findings from various studies on ethambutol optic neuropathy.<sup>5</sup> Several showed a decrease in the RNFL thickness in 20-79% of cases, with significant vision loss due to EON. Two studies representing 68 patients on ethambutol found an increase in RNFL thickness overall and in selected quadrants.<sup>13,14</sup> Han J et al looked at the effect of ethambutol on the ganglion cell-inner plexiform layer (GCIPL) thickness in 37 patients. The one patient that developed EON revealed significant thinning of their GCIPL, whereas all other patients that did not develop EON had no significant changes in their GCIPL.<sup>15</sup> Ju-Yeun et al. showed that the macular ganglion cell-inner plexiform layer (mGCIPL) thickness has a better diagnostic performance in detecting early-onset EON as compared to RNFL thickness.<sup>16</sup> In our study we found that the effect of EON/LON on the thickness of the RNFL also varied. Some patients showed diffuse and/or segmental thickening, while others showed thinning. The hypothesized final common step in EON and LON's pathophysiology is a disruption of oxidative phosphorylation.<sup>2</sup> Initially the dysfunctional oxidative phosphorylation leads to axoplasmic stasis resulting in swelling of the nerve fiber layer. This will present as thickening of the RNFL. With continued toxicity there is consecutive ganglion cell death leading to axonal loss, with subsequent thinning. The RNFL thickness during this stage might fall within the normal range but represents, in fact, swelling of the diminished ganglion cells. Finally, with continued toxicity and extensive ganglion cell loss the RNFL shows thinning. Performing a combined mGCIPL and RNFL might negate this confounding pattern as the mGCIPL is not influenced by RNFL swelling. Another challenging technical aspect was the effect refractive error and axial length had on the angular distribution of the TSNIT (temporal-superior-nasal-inferior-temporal) peaks. This is due to a developmental association of axial myopia and hyperopia on the regional

distribution of the superior and inferior arcuate nerve bundles. In myopia there is a temporal shift in the RNFL peaks while in hyperopia there is a nasal shift.<sup>17</sup> This may lead to a false interpretation of localized thickening or thinning and must be accounted for in the evaluation of these patients. The above-mentioned confounding factors, the lack of data and exact guidelines on the use of RNFL on the diagnosis of EON/LON could be the reason for the low sensitivity of the RNFL. The exact role of RNFL in the investigation of EON/LON is still to be determined and further research on the topic is needed.

Risk factors for the development of EON are dosage, duration of treatment, age above 65 years and renal dysfunction.<sup>5</sup> In our study all “Confirmed Toxicity” patients except for one was using an ethambutol dose above the WHO recommended 15mg/kg. None of the “Confirmed Toxicity” patients had renal dysfunction (except for one that did not have a renal function on the system) or were above the age of 65yrs. Two out of three of the patients on dual treatment developed toxic optic neuropathy. This is in keeping with the current understanding of the pathophysiology of both drugs, with a compounding effect at the common final point of dysfunctional oxidative phosphorylation.<sup>2</sup>

Weaknesses of our study include its retrospective and uncontrolled study design and small sample size. No retinal ganglion cell layer thicknesses were measured to correlate them with those of the RNFL. No visually evoked potentials were performed to correlate with the subjective HVF 24-2 as an objective measure of visual function. However, the study serves only as a pilot to support the use of the Adams D15 as a sensitive screening tool for EON/LON toxicity.

## **Conclusion**

The Adams D15 is a low-cost and sensitive screening tool for the detection of early ethambutol- and linezolid-induced optic neuropathy.

## **Acknowledgments**

Groote Schuur Hospital clinical, technical and nursing colleagues who assisted in performing the tests and investigations involved in the study, as well as the interpreters who helped explain the nature of the tests.

### Table Legends

Table I. Toxicity groups and treatment regimens of patients who were screened for EON and LON

Table II. Sensitivities and positive predictive values of the Adams D15, FM D15, HVF 24-2 and RNFL-OCT tests

Table III. Raw data of all the patients in the “Confirmed Toxicity” group

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Tables are included below as pictures in this Mmed submission but have been submitted as jpegs to the South African Journal of Ophthalmology as per publication guidelines.

<b>Table I</b>	<b>Toxicity groups and treatment regimens of patients who were screened for EON and LON</b>			
	<b>Patients screened</b>	<b>"No Toxicity"</b>	<b>"Uncertain toxicity"</b>	<b>"Confirmed toxicity"</b>
<b>Total</b>	15	6	3	6
<b>Linezolid</b>	7	3	3	1
<b>Ethambutol</b>	5	2	0	3
<b>Both</b>	3	1	0	2

<b>Table II</b> Sensitivity and positive predictive values of the Adams D15				
	<b>Eyes with TON</b>	<b>Eyes without TON</b>	<b>Total</b>	
<b>Positive Adams D15</b>	12	1	13	PPV = 92%
<b>Negative Adams D15</b>	0	11	11	
<b>Total</b>	12	12	24	
Sensitivity = 100%				
<b>Sensitivity and positive predictive values of the FM D15</b>				
	<b>Eyes with TON</b>	<b>Eyes without TON</b>	<b>Total</b>	
<b>Positive FM D15</b>	10	1	11	PPV = 91%
<b>Negative FM D15</b>	2	11	13	
<b>Total</b>	12	12	24	
Sensitivity = 83%				
<b>Sensitivity and positive predictive values of the HVF 24-2</b>				
	<b>Eyes with TON</b>	<b>Patients without TON</b>	<b>Total</b>	
<b>Positive HVF 24-2</b>	11	0	11	PPV = 100%
<b>Negative HVF 24-2</b>	1	12	13	
<b>Total</b>	12	12	24	
Sensitivity = 92%				
<b>Sensitivity and positive predictive values of the RNFL thickness</b>				
	<b>Eyes with TON</b>	<b>Patients without TON</b>	<b>Total</b>	
<b>Positive RNLF</b>	8	0	8	PPV = 100%
<b>Negative RNFL</b>	4	10	14	
<b>Total</b>	12	10	22	
Sensitivity = 67%				
TON: Toxic optic neuropathy, PPV: Positive predictive value				

<b>Table III</b>	Raw data of all the patients in the "Confirmed Toxicity" group					
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (Years), Gender	38, Male	33, Female	27, Female	38, Male	62, Male	36, Male
Presenting symptoms (VA: Visual acuity)	Decreased VA for 3/12	Decreased VA for 3/52	Decreased VA for 1/12	Decreased VA for 1/52	Decreased VA for 1/52	Decreased VA for 3/52
Renal function	Normal	Normal	Not available	Normal	Normal	Normal
HIV status,	Positive	Positive	Negative	Negative	Negative	Negative
Taking ARV's	Yes	Yes	Not applicable	Not applicable	Not applicable	Not applicable
Type of TB	Disseminated	Disseminated	Pulmonary	*Pre-XDR	†XDR	‡MDR
Duration of Ethambutol (E) / Linezolid (L) treatment (Months)	E: 4 months	E: 8 months	E: 6 months	L: 2 months	E: 4 months L: 4 months	E: 35 months L: 3 months
Dosage (Mg/kg)	17.6	15	21.2	600mg bd	E: 21mg/kg L: 600mg bd	E: 20mg/kg L: 600mg bd
<b>Examination (OD on top, OS bottom)</b>						
<b>Visual acuity</b> (CF: Counting fingers)	6/36 6/36	CF CF	6/12 6/36	CF CF	CF CF	6/9 6/6
<b>FM D15</b>	Passed	Failed	Failed	Failed	Failed	Failed
	Passed	Failed	Failed	Failed	Failed	Failed
<b>Adams D15</b>	Failed	Failed	Failed	Failed	Failed	Failed
	Failed	Failed	Failed	Failed	Failed	Failed
<b>HVF</b>	Unable to do	Unable to do	<u>Cecocentral scotoma</u>	<u>Cecocentral scotoma</u>	Central scotoma	<u>Cecocentral scotoma</u>
			<u>Cecocentral scotoma</u>	<u>Cecocentral scotoma</u>	Central scotoma	Paracentral scotoma
<b>RNFL</b>	Failed	Passed	Failed	Failed	Failed	Passed
	Passed	Passed	Failed	Failed	Failed	Passed
<p>*Pre-XDR: TB with resistance to isoniazid and rifampicin and either a fluoroquinolone or a second line injectable agent but not both.  †XDR: TB with resistance to isoniazid and rifampicin, plus any fluoroquinolone and at least one of the three injectable second-line drugs.  ‡MDR: TB with resistance to isoniazid and rifampicin.</p>						

## **Part B: The Literature review**

### **The literature review: Is the Adams D-15 colour vision test a sensitive screening tool for ethambutol- and linezolid-induced optic neuropathy? A retrospective case series**

#### **Introduction**

Ethambutol hydrochloride is a commonly used first-line anti-tuberculous agent. Although rare, ocular toxicity in the form of ethambutol-induced optic neuropathy (EON) has been well-documented since its first use in the 1960's.<sup>1</sup>

Classically described as dose- and duration-dependent, as well as being reversible on discontinuation, true reversibility of EON remains controversial. At the standard World Health Organization (WHO) recommended daily dose of 15mg/kg, the incidence of toxicity is approximately 1%.<sup>1</sup>

Linezolid is a core second-line drug used in the treatment of Multidrug Resistant Tuberculosis. The exact incidence of toxicity in the form of Linezolid-induced Optic Neuropathy (LON) is uncertain, due to its frequency of use increasing only in recent years. Two recent meta-analyses have reported prevalence rates between 8 and 13.2%.<sup>2,3</sup>

Unlike ethambutol, linezolid toxicity has been shown to be predominantly duration dependant. Recovery of visual function is also more substantial.<sup>2,3</sup>

South Africa has one of the highest burdens of tuberculosis (TB) worldwide. In 2019, the estimated incidence was 360 000 new cases per year.<sup>4</sup> Taking these numbers into consideration, 3600 patients will develop a potentially blinding EON annually in South Africa, unless toxicity is detected in a timely fashion. This number runs into hundreds of thousands globally.<sup>5</sup>

International guidelines on the prevention and early detection of EON have been published, but opinion is divided regarding the clinical effectiveness of regular vision tests to enable early detection of toxicity.<sup>1,5</sup> It has been recommended that all asymptomatic patients taking ethambutol should receive monthly screening for signs of EON that should include at least visual acuity and Amsler grid testing. However, the clinical burden of screening following these recommendations is not manageable in TB endemic, low-resource settings such as South Africa. Although visual evoked potentials (VEP) and optical coherence tomography (OCT) have been proposed to screen for subclinical EON, the validity, reliability, and reproducibility of screening with these modalities has not been well studied.<sup>5</sup> Currently there is no low-cost and sensitive screening tool for EON and there are no accepted guidelines on the prevention and early detection of LON.<sup>6</sup>

The aims of this study were therefore to evaluate the ability of the low-cost Adams desaturated D15 (Adams D15) colour vision test to detect early EON and LON, as well as to document the clinical features of patients who were screened for EON and LON at a single South African tertiary referral centre.

## **Literature search strategy**

Pubmed was the only database used except for TB statistics of South Africa. The search parameters were broadly set and Pubmed searches were repeated at regular intervals through the evolution of the project. The final search was done in March 2021.

The search terms used were: Ethambutol toxic optic neuropathy, Ethambutol optic neuropathy, Linezolid toxic optic neuropathy, Linezolid optic neuropathy, Toxic optic neuropathy, Adams D15 colour vision test, Lanthony desaturated D15 colour vision test, TB statistics South Africa and Optical coherence tomography.

The resulting abstracts were read, reviewed and the full article was acquired if the abstract appeared to be relevant. Only English language publications were used which may have resulted in publication bias.

## **Literature on EON and LON**

A review article by Chamberlain *et al* (2017) stated that ethambutol is a bacteriostatic drug used in the treatment of Mycobacterium species. It acts as a metal chelator which prevents cell wall synthesis in mycobacteria by inhibiting arabinosyl transferase. The exact mechanism of EON remains unknown, but it has been hypothesized that it results from a disrupted oxidative phosphorylation secondary to decreased available copper in human mitochondria, or an inhibited lysosomal activation due to chelation of zinc.

Metha *et al* (2016) reported on a retrospective cohort of 86 patients initiated on linezolid-containing drug resistant TB treatment. Metha *et al* (2016) stated that Linezolid is a bacteriostatic synthetic oxazolidinone antibiotic used in the treatment of mycobacterial infections, including multi-drug resistant tuberculosis (MDR-TB). It acts by inhibiting bacterial protein synthesis through the inhibition of the 50s ribosomal subunit of the bacterial DNA. Human somatic DNA does not resemble 50s ribosomal DNA. On the other hand, human mitochondrial DNA more closely resembles the 50s ribosomal subunit, thus mitochondrial protein synthesis is disrupted that leads to a disruption in oxidative phosphorylation. Any tissue that has an exceedingly high energy demand will be most affected, including the optic nerve and more specifically the macular-papular bundle supplying central high-resolution vision.

As stated by Chamberlain *et al* (2017) and Metha *et al* (2016) the final pathway of disease caused by ethambutol and linezolid is through mitochondrial dysfunction, leading to a disruption in oxidative phosphorylation. Thus, the clinical picture of toxicity and the screening tests used to detect them are similar. The main risk factor for EON is dosage:

Estimated prevalence of ethambutol-induced optic neuropathy at various doses <sup>5</sup>	
Ethambutol dose (mg/Kg per day)	Estimated prevalence (%)
≤15	Less than 1
20	3
25	5-6
>35	18-33

Chamberlain *et al* (2017) also noted other risk factors for the development of EON including duration of treatment, age over 65 years, renal disease and concomitant use of isoniazid therapy. EON may begin rapidly between 1 and 36 months after starting treatment but most patients experience visual symptoms within the first 9 months. Renal disease might lead to higher serum levels and toxicity because ethambutol is excreted by the kidneys.

Dempsey, Sickman, Slagle (2018) conducted a retrospective analysis of 39 cases of LON. Dempsey, Sickman and Slagle stated that the main risk factor for LON is the duration of treatment. Linezolid is approved by the United States Food and Drug Administration for a maximum of 28-day use. For this duration there are very minor side effects. However, in the treatment of MDR-TB it is used off-label for much longer periods of time. The vast majority of patients develop symptoms of toxicity between 90 and 365 days. The median time to first symptom presentation is 240 days ( $\pm 7$  months).

Metha *et al* (2016) and Dempsey, Sickman, Slagle (2018) reported that there was a strong correlation shown between linezolid clearance and creatinine clearance as well as that the oxidation of Linezolid takes place in the liver but does not involve the cytochrome P450 system. They inferred that despite there being no other proven risk factors for toxicity, clearance by the kidney and metabolism by the liver most likely play a role.

The reviews by Rucker *et al* (2006) and Chamberlain *et al* (2017) stated that EON and LON clinically present with vision loss, dyschromatopsia, optic disc swelling and eventual optic atrophy. Vision loss is typically subacute, bilateral, symmetrical, central, and painless. Color vision abnormalities include difficulty distinguishing between red and green as well as blue and yellow. With early toxicity the optic nerve appears normal on fundus examination but with advanced toxicity optic disc pallor ensues. In the reviews by Chan, Kwok (2006) and Chamberlain *et al* (2017) it was stated that if EON were to be detected early and with prompt discontinuation of ethambutol, 30-64% of patients showed visual improvement over a period of several months. Few patients showed full recovery with the average being 2 lines on the Snellen Chart. Age was a prognostic factor for recovery, with improvement seen in only 20% of patients older than 60 years and 80% of patients younger than 60 years.

Dempsey, Sickman, Slagle (2018) reported that as with ethambutol, early detection of LON with prompt discontinuation of linezolid will give the best chance for recovery. Unlike ethambutol, most patients will show a full recovery with a recent study reporting that 91% of patient's vision recovered to 20/40 or better. The time to the onset of symptoms may show a susceptibility to toxicity as patients that develop symptoms within the first 60 days of treatment had a much less significant recovery.

## **Literature on the international screening guidelines for EON and LON**

Chamberlain *et al* (2017) reported on the international guidelines of self screening and healthcare provider screening. Chamberlain stated that for patients on ethambutol to perform self screening they should be educated on the possibility of visual loss and thus the need for immediate follow if visual changes should occur. Patients should be provided with a pocket Snellen chart or Amsler grid to perform self screening at home. Healthcare provider screening includes baseline examinations immediately prior to, or at the time of ethambutol treatment initiation which include visual acuity, formal visual field testing, dilated funduscopy and color vision testing. High-risk patients should preferably be screened monthly by an eye care specialist.

Dempsey, Sickman, Slagle (2018) reported that there are currently no accepted guidelines on the prevention and early detection of LON.

## **Literature on the tests used to screen for EON and LON**

### **Visual acuity, stereo acuity, and contrast sensitivity**

The review by Chamberlain *et al* (2017) stated that patients presenting with clinical EON typically complain of subacute, bilateral, painless, and typically symmetrical loss of central vision.

Menon *et al* (2009) conducted a prospective study of 104 eyes of 52 patients being treated with ethambutol for 60 days in a Directly Observed Treatment Strategy Centre. Visual acuity, visual fields, visual evoked responses, stereoacuity and RNFL on OCT were assessed. Assessments were performed before start of therapy, after 1 and 2 months of treatment and 1 month after stopping ethambutol. Early toxicity was detected in a total of 19.23% of eyes as evidenced by abnormality on one or more of the visual fields, visual evoked responses or RNFL on OCT. None of the eyes showing early EON had any deficit in visual acuity, color vision, stereoacuity or fundus examination.

### **Fundus examination of the optic nerve head**

The review by Chamberlain *et al* (2017) reported that with early EON the optic nerve appears normal on fundus examination, but that after advanced damage has occurred due to clinical EON, optic disc pallor will develop. If optic atrophy is present at onset, it is generally considered a poor prognostic sign.

## Color vision tests

### **Ishihara pseudoisochromatic plates (Ishihara), Farnsworth Munsell D15**

The review by Chan, Kwok (2006) stated that subtle blue-yellow defects caused by early EON could only be detected using the Lanthony Desaturated color vision test (Lanthony D15), not the Ishihara pseudoisochromatic plates (Ishihara) nor the Farnsworth Munsell D15. Menon *et al* (2009) came to a similar conclusion when 19.23% of the 104 eyes of 52 patients receiving 60 days of ethambutol showed early EON but none of the patients showed early toxicity on the Ishihara.

Cruz *et al* (2010) conducted a prospective single-cohort study involving 128 eyes of 64 newly diagnosed patients with category 1 tuberculosis, recruited from Directly Observed Treatment Strategy health centers in Manila. All patients received 60 days of ethambutol treatment. 47.88% showed early toxicity on the Lanthony D15. None of the patients showed early toxicity on the Ishihara and only one patient showed early EON on their Farnsworth Munsell D15.

### **Lanthony desaturated D15 (Lanthony D15)**

The Lanthony D15 was developed to test for subtle color discrimination losses, which can accompany eye disease. The test is similar in design to the Farnsworth Munsell D15, but the colors are less saturated by 2 units of Munsell Chroma and lighter by 3 units of Munsell Value.

As stated above by Chan, Kwok (2006), subtle blue-yellow defects caused by early EON could only be detected using the Lanthony D15 not the Ishihara nor the Farnsworth Munsell D15. A similar result was found by Cruz *et al* (2010), when 47.88% of 128 eyes of 64 patients receiving 60 days of ethambutol showed early EON on the Lanthony D15 while only one patient showed toxicity on their Farnsworth Munsell D 15.

Good, Schepler, Nichols (2005) evaluated the reliability of the Lanthony D15 test by testing 126 normal patients 1 month apart. Good, Schepler, Nichols (2005) concluded that although the Lanthony D15 test can be used to assess fine color discrimination, there is considerable within-subject variability in test results. The intraclass correlation coefficient was less than that recommended for use in clinical testing or research. Good, Schepler, Nichols (2005) recommended that clinicians should consider at least three administrations of the test at each sitting to ensure precision and use the mean of those three tests.

## Visual fields

The reviews by Chan, Kwok (2006) and Chamberlain *et al* (2017) stated that central or cecentral scotomas are the most common visual field defects found in EON, but that bitemporal defects or peripheral field constriction have also been reported.

As per Menon *et al* (2009), a total of 19.23% of the 104 eyes of 52 patients receiving 60 days of ethambutol showed early EON. Eight of 104 (7.69%) eyes showed visual field defects, half of which returned to normal once the ethambutol was stopped.

## **Optical Coherence Tomography (OCT)**

### **Retinal nerve fiber layer (RNFL) & Ganglion cell-Inner plexiform layer (GCIPL) thickness**

OCT has only been evaluated as a tool for detecting EON in a handful of small studies to date.

Several studies used OCT to detect changes in the peripapillary retinal nerve fiber layer (RNFL) of patients with clinically significant vision loss from clinical EON. These studies, including a prospective case series of 5 patients with clinical EON by Kim, Hwang (2009) and a prospective case series of 3 patients with clinical EON by Zoumalan, Agarwal, Sudan (2005) who demonstrated a decrease in RNFL thickness of 20-79%. Chai, Foroozan (2007) found similar results in a retrospective case series of 8 patients with a history of clinical EON who were examined within 3 months after stopping ethambutol treatment. A decrease in RNFL was observed in all quadrants in patients with clinical EON who had recently discontinued the medication. This decrease was most pronounced in the temporal quadrant of the optic disc.

The prospective study by Menon *et al* (2009) found a total of 19.23% of the 104 eyes of 52 patients receiving 60 days of ethambutol showed early EON. Three of 104 eyes (2.88%) showed temporal thinning of the RNFL. At 1 month after stopping ethambutol all three eyes demonstrated residual latency on VEP and residual visual field defects.

The review by Chamberlain *et al* (2017) reported on two studies representing 68 patients taking ethambutol and found that early EON led to an increase in RNFL thickness overall or in select quadrants. A prospective longitudinal cohort by Han *et al* (2015) found one out of 37 patients treated for pulmonary tuberculosis developed early EON. In this patient, thickening of the RNFL and thinning of the GCIPL were noted at the onset of symptoms. After discontinuation of ethambutol, RNFL and GCIPL thickness progressively normalized.

Chamberlain *et al* (2017) stated that in addition to damage to the RNFL, experiments in animal models have demonstrated toxicity of the GCIPL.

Ju-Yeun *et al* (2019) evaluated 28 eyes of 15 patients with clinical EON and 100 eyes of 53 healthy control subjects with OCT to evaluate the RNFL's and GCIPL's area under the receiver operating characteristic (AUROC) curve sensitivity to detect EON. The AUROC of the average GCIPL (0.812) thickness was significantly greater than that of the average RNFL (0.507) thickness ( $p < 0.001$ ). Ju-Yeun *et al* (2019) concluded that in challenging cases of EON, the GCIPL thickness has better diagnostic performance in detecting early-onset EON as compared with using RNFL thickness. Among the early detection ability of GCIPL thickness, minimum GCIPL thickness has high diagnostic ability.

A literature review by John, Randy, Kardon (2016) stated that there is developmental association between axial myopia and hyperopia on the regional distribution of the superior and inferior arcuate

nerve bundles. In myopia there is a temporal shift in the RNFL peaks while in hyperopia there is a nasal shift. This may lead to a false interpretation of localized thickening or thinning and must be accounted for in the evaluation of these patients.

Chamberlain *et al* (2017) concluded that although OCT is likely to be able to detect significant RNFL and possibly GCIPL thickness changes in patients with clinical EON, it may or may not be useful in screening patients for subclinical disease while on ethambutol therapy. More research is needed to adjudicate this question and establish OCT screening guidelines for EON.

## **Visual evoked potentials (VEP)**

Visual evoked potentials are small electrical signals generated in the occipital cortex following a brief visual stimulus. The p100 wave is a positive deflection that occurs on an average 100ms after the visual stimulus. An increased latency of the p100 is a well-established tool in the diagnosis of optic nerve disease such as optic neuritis, though the exact amount that constitutes an abnormality varies by machine.

Chamberlain *et al* (2017) reviewed several studies and found increased p100 wave latency in patients diagnosed with EON. Chamberlain *et al* concluded that taken together these results show promise for the utility of VEP for EON screening, but more research is needed to better understand its usefulness for this purpose clinically.

## **Multifocal Electroretinogram (Mf-ERG)**

Chamberlain *et al* (2017) reviewed 4 case series representing nine patients that showed decreased amplitude of Mf-ERG waves in the central and nasal macular regions of patients with vision loss while taking ethambutol. In two larger studies of 17 and 44 patients taking ethambutol the researchers found decreased P1 amplitude and delayed P1 latency. None of the patients in these studies developed visual symptoms, suggesting the ability of Mf-ERG to detect early EON. Chamberlain concluded that more research is needed to understand the role Mf-ERG should play in the detection of early EON in patients taking ethambutol.

## **Literature on the Adams D15**

The Adams desaturated D15 (Adams D15) colour vision test was introduced to provide a test for acquired colour vision defects that is more sensitive than the standard Farnsworth D-15 and quicker to administer than the Farnsworth-Munsell 100 hue test. The test is similar in design to the Farnsworth Panel D-15, but the colors are less saturated by 2 units of Munsell Chroma. The colour plates of the Adams are thus in between that of the Farnsworth Munsell D15 and the Lanthony desaturated D15 in terms of Munsell Chroma and Munsell Value.

Adams *et al* (1982) evaluated 19 glaucoma subjects and 19 glaucoma-suspects with the Farnsworth Munsell D15 and Adams D15. Each patient was individually age matched to within 4 years with a normal

control subject. In pilot studies they found that patients with retinal disorders frequently made multiple errors that did not meet the conventional failure criteria (2 crossings or more), whereas normal patients rarely made more than one transposition error. Consequently, they decided to evaluate patients using the conventional and above-mentioned modified failure criteria (More than a single transposition). During their study they found that the modified criteria improved test sensitivity without a significant loss of specificity. When the conventional criteria were used, 4 glaucoma subjects and 1 glaucoma-suspect failed the FM D15. When the modified criteria were used, 10 glaucoma patients and 6 glaucoma suspects failed the FM D15. The Adams D15 with modified failure criteria was even more sensitive with 14 glaucoma patients and 11 glaucoma suspects failing the Adams D15. None of the age matched normal patients (mean age between 51-54 years) failed the FM D15, while 11% failed the Adams D15. To better estimate the failure rate in the general population the FM D15 and Adams D15 was also performed on 72 normal patients with a mean age 35yrs. Of the 72 normal patients 1% failed the FM D15 and 5% failed the Adams D15.

Hovis, Ramaswamy, Anderson (2004) evaluated 100 patients with normal colour vision and 64 patients with congenital red-green colour defects with the Adams D15. Each patient was evaluated twice with an interval of at least 10 days apart to assess the reliability and repeatability of the Adams D15. When the above-mentioned modified failure criteria was used, 1-3% of the patients with normal colour vision failed with low repeatability for failing the second time but good repeatability for passing. When applying the modified failure criteria to patients with congenital red-green colour defects the test results were repeatable for 60% of patients, with approximately 12% who failed the first session improving to a pass on retest and approximately 10% changed to a failing result on the retest.

## **Summary**

A consequence of the treatment for the current epidemic of TB in South Africa, is the real risk of permanent visual loss due to EON and LON. The clinical burden following the current international guidelines is not manageable in TB endemic, low-resource settings such as South Africa.

Once clinical EON has set in the evidence shows that patients have a component of permanent damage that they will never recover from. LON's recovery is more significant than that of EON.

Visual acuity, Farnsworth Munsell D15 and Ishihara have been shown to detect clinical EON/LON but not early or subclinical EON/LON.

The Lanthony D15 has been shown to be able to detect early/subclinical EON but its reliability and repeatability has been shown to be too low to use in a clinical setting.

Visual Fields have shown to be sensitive for picking up early or subclinical EON/LON.

OCT, VEP and Mf-ERG have been shown to be sensitive for picking up early or subclinical EON/LON but more research is required to define their role in screening for EON/LON.

The Adams D15 with modified failure criteria has been shown to be more sensitive than the Farnsworth Munsell D15 in detecting colour vision abnormalities in glaucoma patients and glaucoma suspects without the loss of specificity. It has also been proven to have good reliability and repeatability indices.

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## **Part 3: Addendum**

- South African Ophthalmology Journal publication guidelines