



Moorfields Eye Hospital
NHS Trust

Use of anti-VEGFs in Resource Poor Settings

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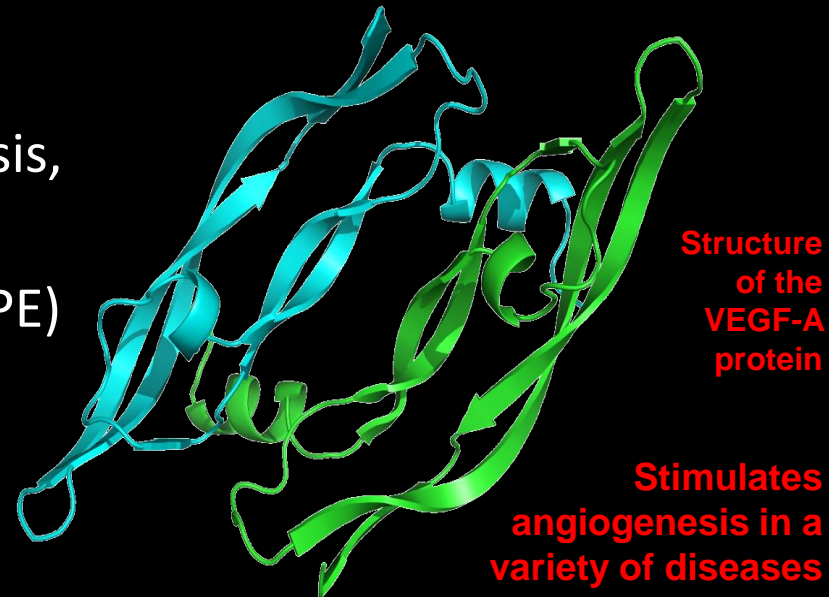
What is Vascular Endothelial Growth Factor (VEGF)?

Normal physiology

- Regulates angiogenesis in embryogenesis, skeletal growth, and reproduction ¹
- Found in retinal pigment epithelium (RPE) maintains healthy endothelium²

Pathological angiogenesis

- Angiogenesis in tumours
- Intraocular neovascularisation¹
 - VEGF localised in choroidal neovascular membranes in AMD
 - VEGF over-expression from RPE associated with AMD neovascularisation²
- Associated with vascular permeability and oedema formation³
- Therapeutic target in oncology and ophthalmology



1. Ferrara N et al. *Nat Med.* 2003;9(6):669-676.

2. Witmer AN et al *Prog Retin Eye Res* 2003;23(1):1-29.

3. Rudge JS et al. In: *Angiogenesis: An Integrative Approach From Science to Medicine.* 2008:415-420.

4. Research Collaboratory for Structural Bioinformatics Protein Data Bank. <http://www.pdb.org>. Accessed September 25, 2012

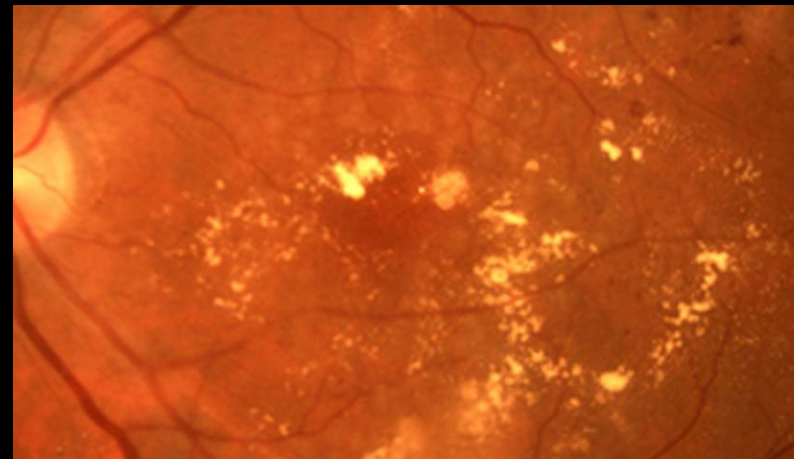
5. Muller YA et al. *Structure.*1998;6:1153-1167.

Classification of diabetic macular oedema (DMO)

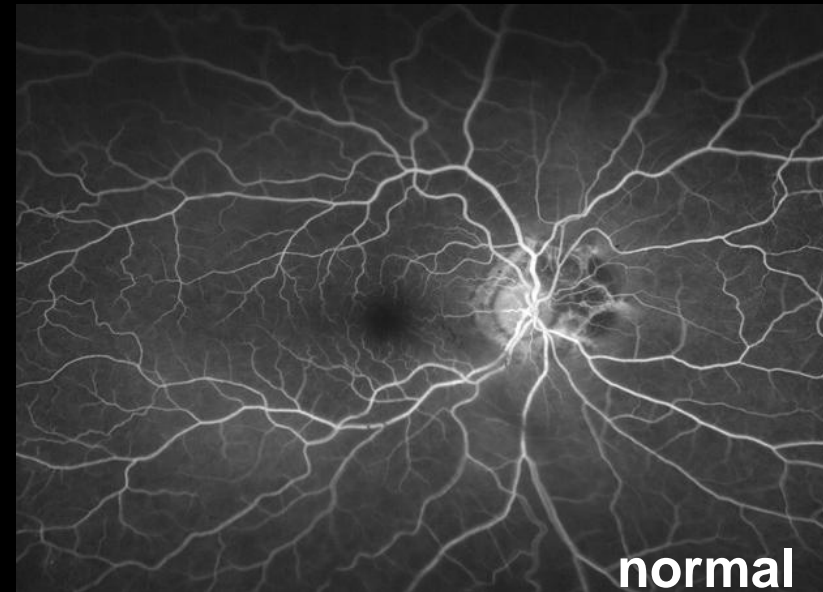
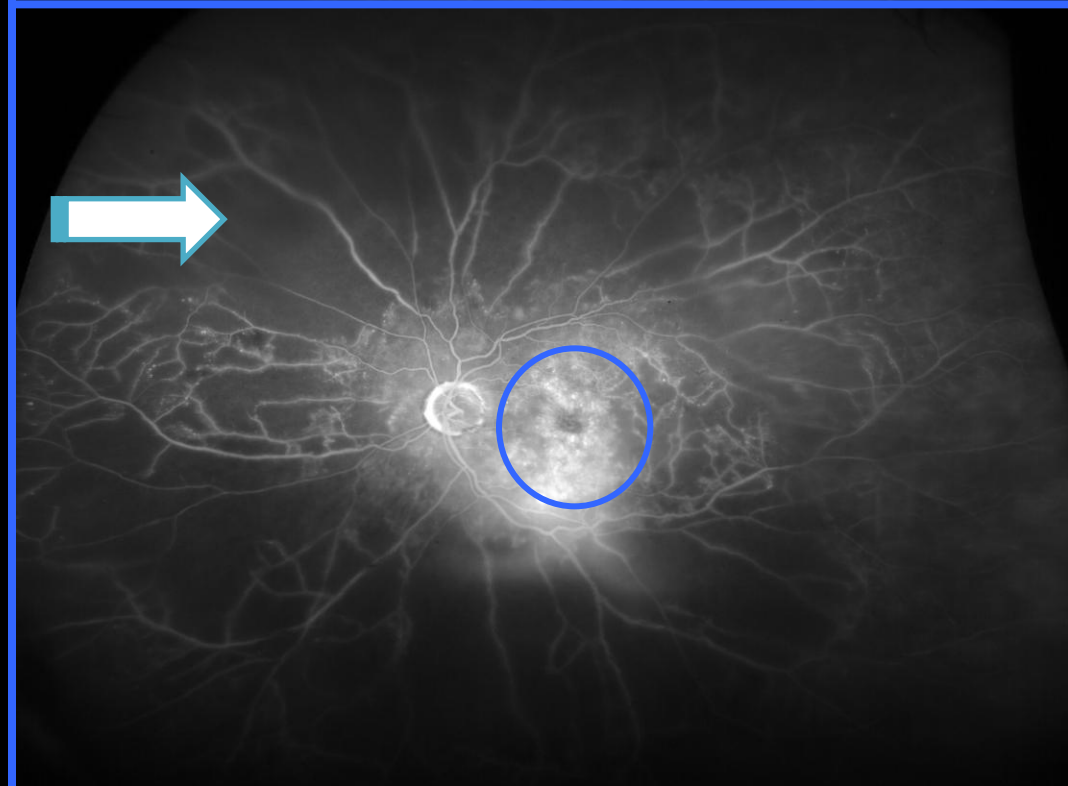
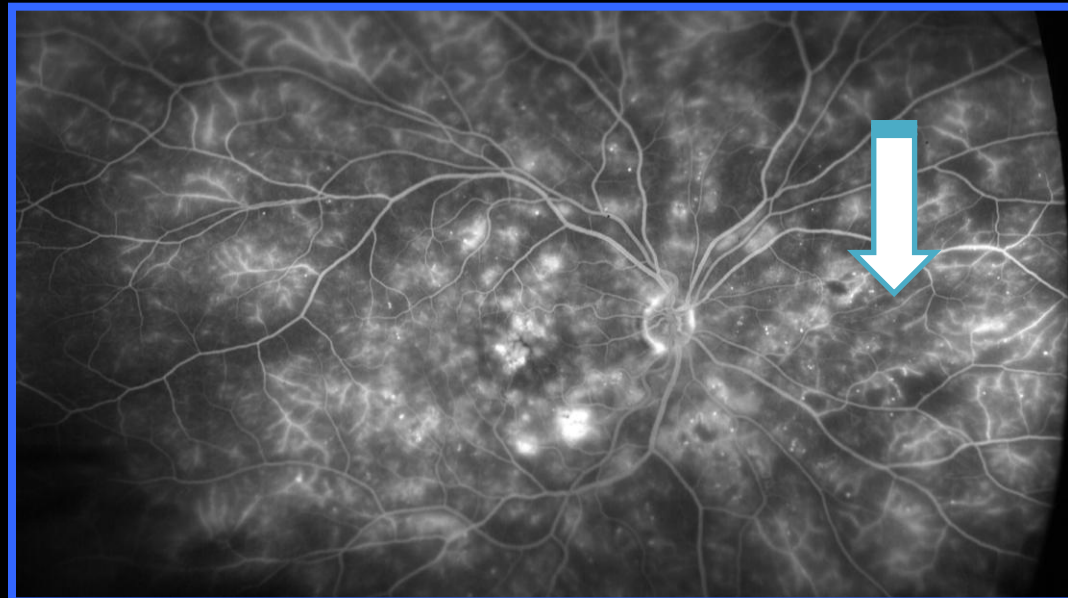
- DMO can occur at any stage of diabetic retinopathy, but is mainly associated with severe non-proliferative and proliferative DR
- Currently DMO is classified as focal or diffuse
 - **Focal DMO:** caused by focal leakage from retinal microaneurysms and dilated capillary segments
 - **Diffuse DMO:** caused by leakage from diffusely dilated retinal capillaries throughout the posterior pole



Diabetic maculopathy with haemorrhages and circinate exudates - NSC grade M



Retinal Angiograms in DMO

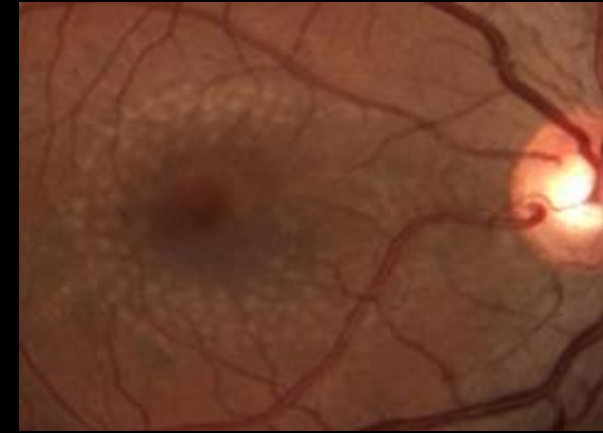
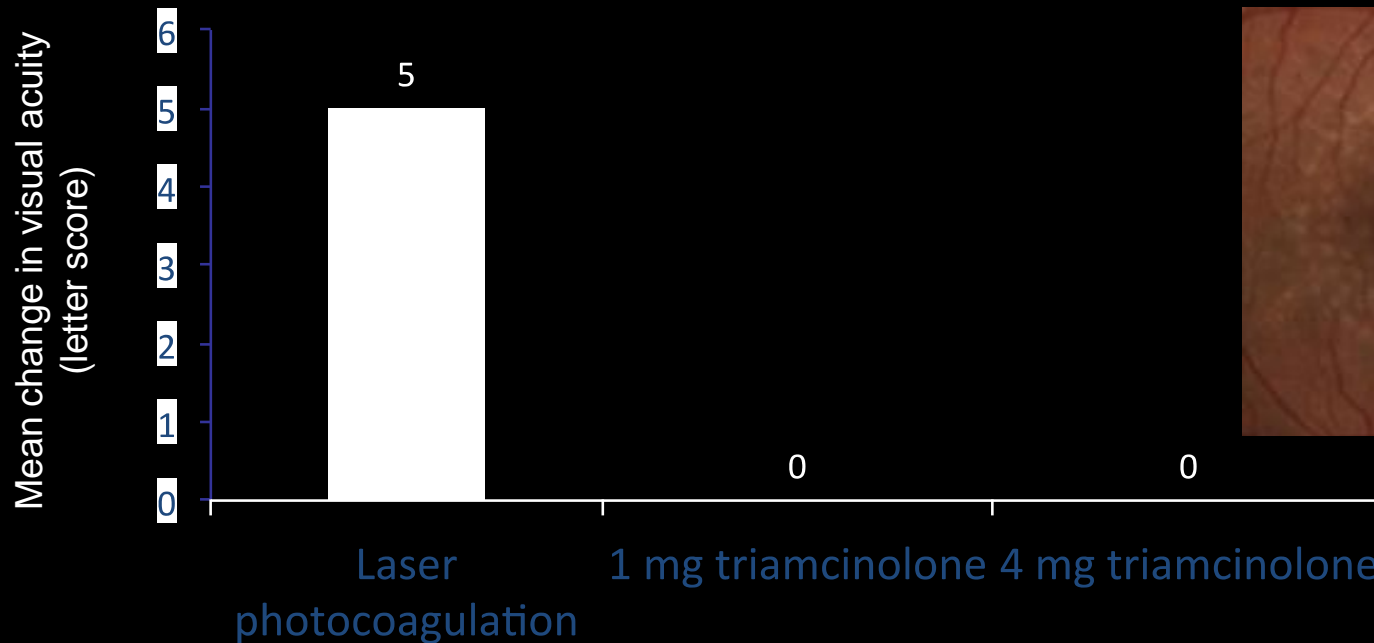


Raised hydrostatic pressures,
hyper-permeability

Hyperglycaemia and hypoxia
upregulate growth factors
including VEGF

Laser photocoagulation vs. intravitreal triamcinolone acetonide in DMO

Mean change in visual acuity from baseline to 3 years according to treatment group¹

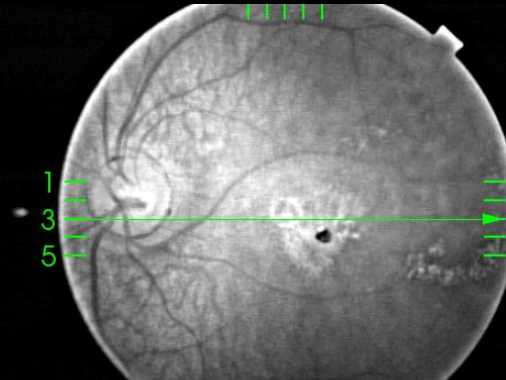
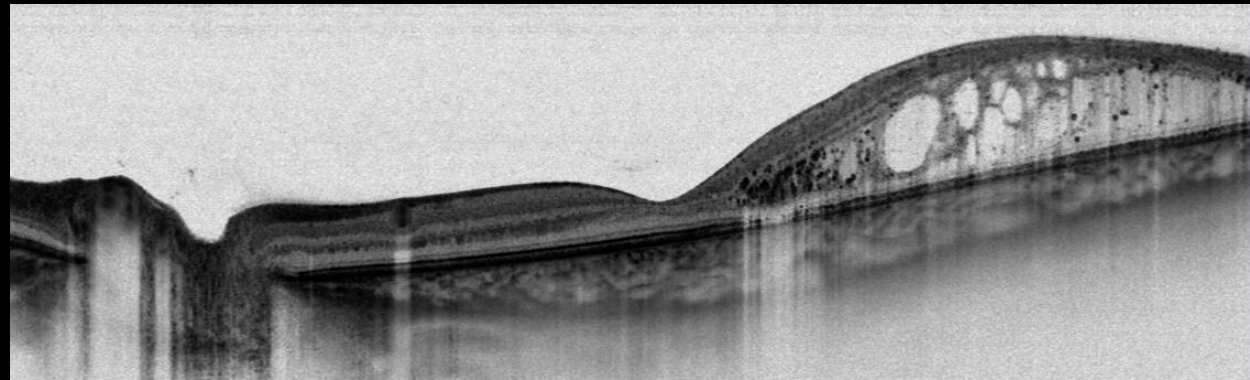


Elevated eye pressure and a requirement for cataract surgery was more frequent in eyes treated with triamcinolone than laser photocoagulation²

1. Beck *et al.* *Arch Ophthalmol* 2009;127:245–51

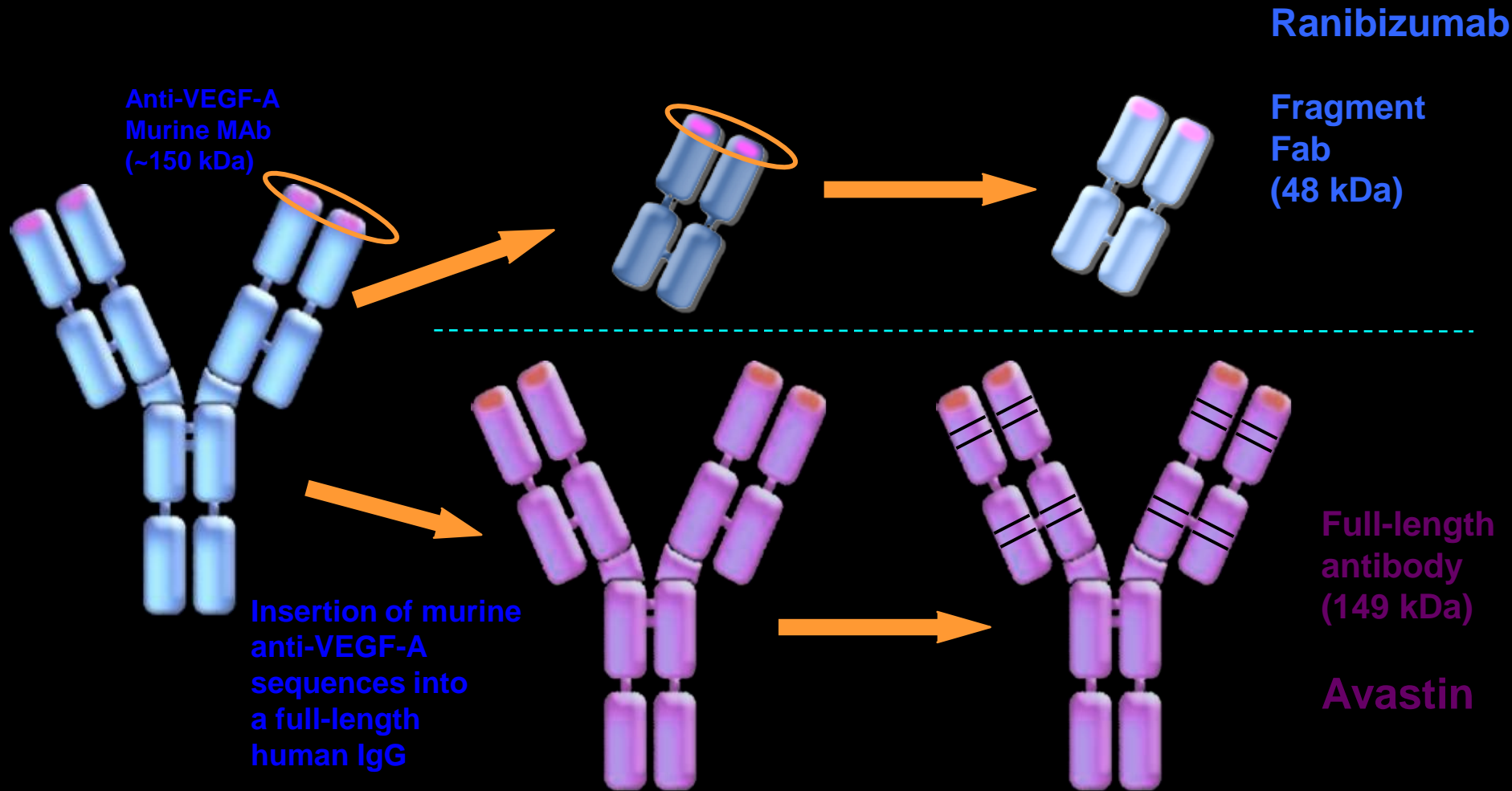
2. Diabetic Retinopathy Clinical Research Network. *Ophthalmology* 2008;115:1447–9

Diffuse DMO resistant to Laser



- VEGF levels are elevated in the vitreous and retina of patients with diabetic retinopathy
- VEGF increases vascular permeability by affecting tight junction proteins

Lucentis [ranibizumab] and Avastin [bevacizumab]



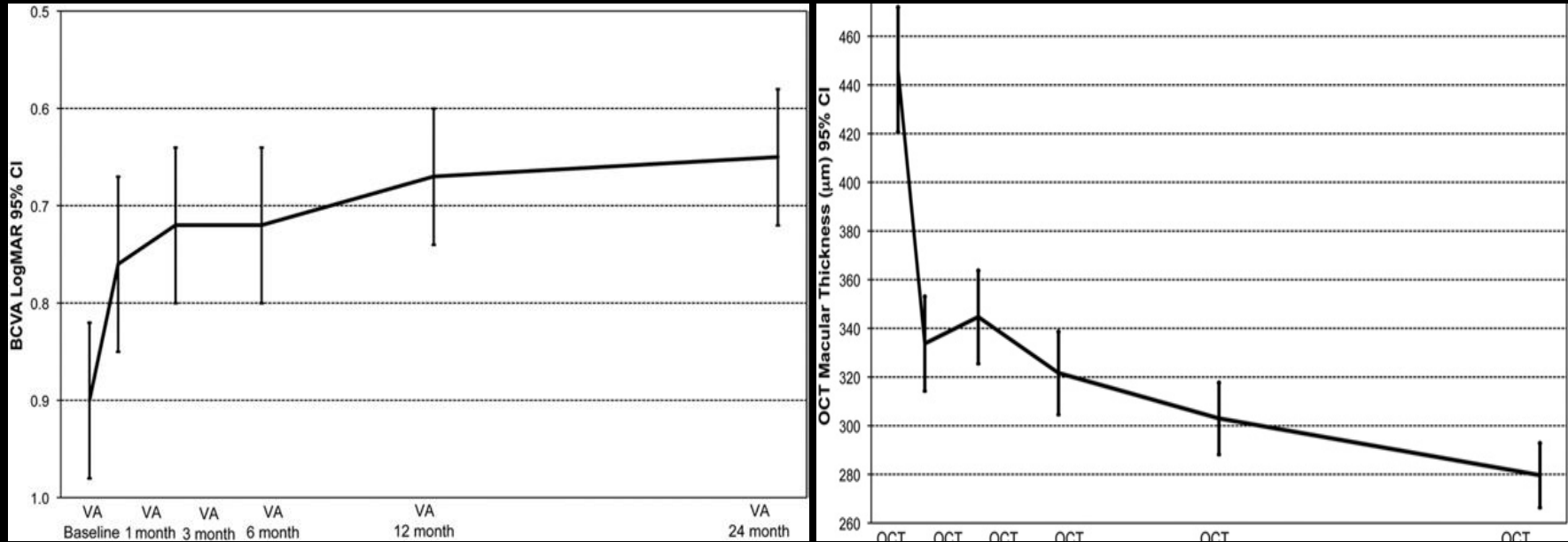
Avastin (bevacizumab)

- Developed to treat colorectal cancer – intravenous avastin
- Avastin usage in the eye is “off license”
- While Lucentis being developed, the use of Avastin spread internationally and accessed by some resource-poor countries
- Dividing a vial allows cheap production of a dose which can be used in the eye



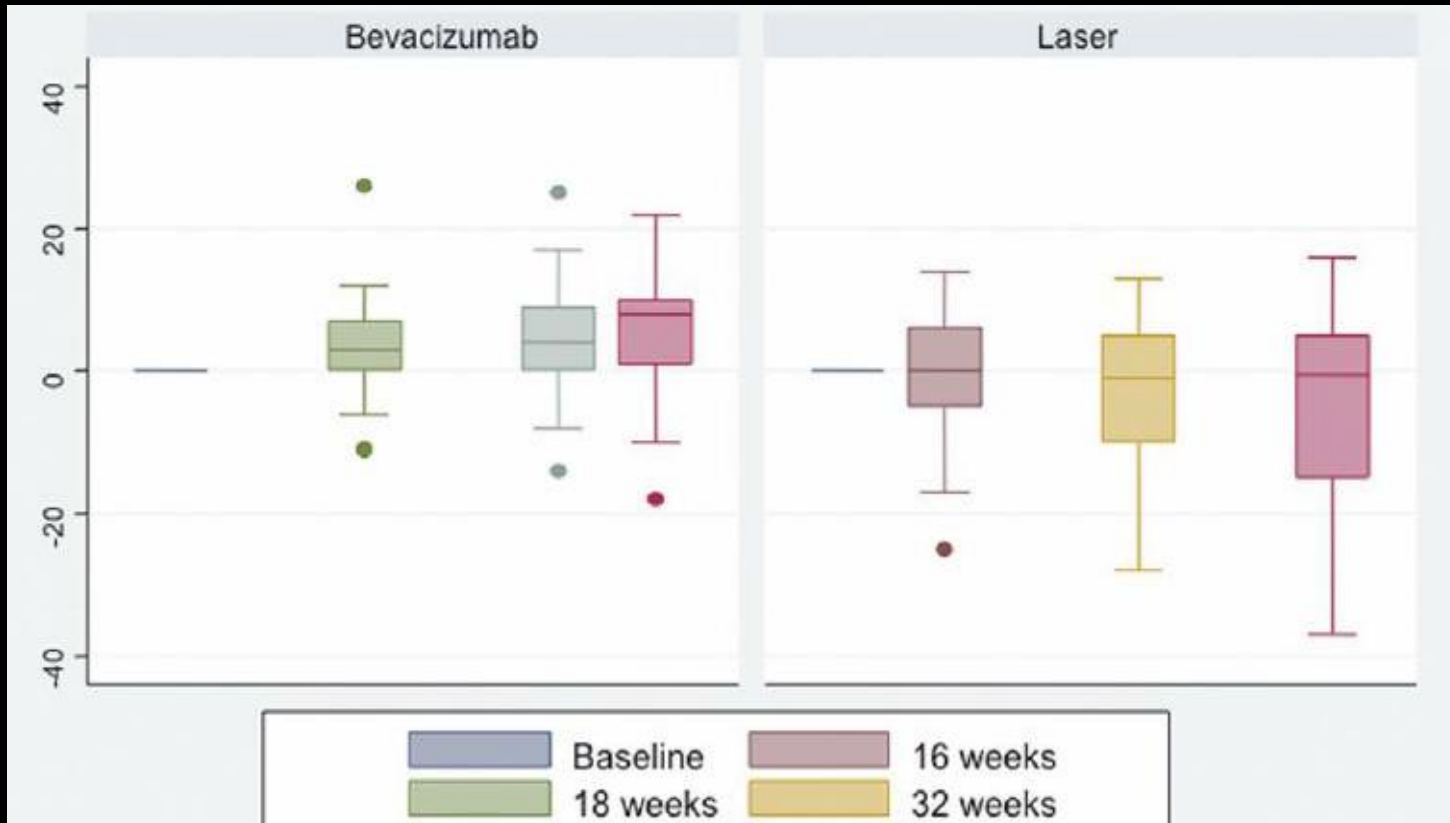
Primary Intravitreal Avastin for Diffuse DMO

The Pan-American Retina Study (at 2 years)



- Vision improved at 1 month ($P<0.001$) and maintained over 2 years
- Foveal thickness: Rapid reduction within 4 weeks
Sustained improvement over 2 years from 446 to 280µm ($P<0.001$)
- Mean number of injections per eye was 5.8 (range, 1–15)

BOLT Study



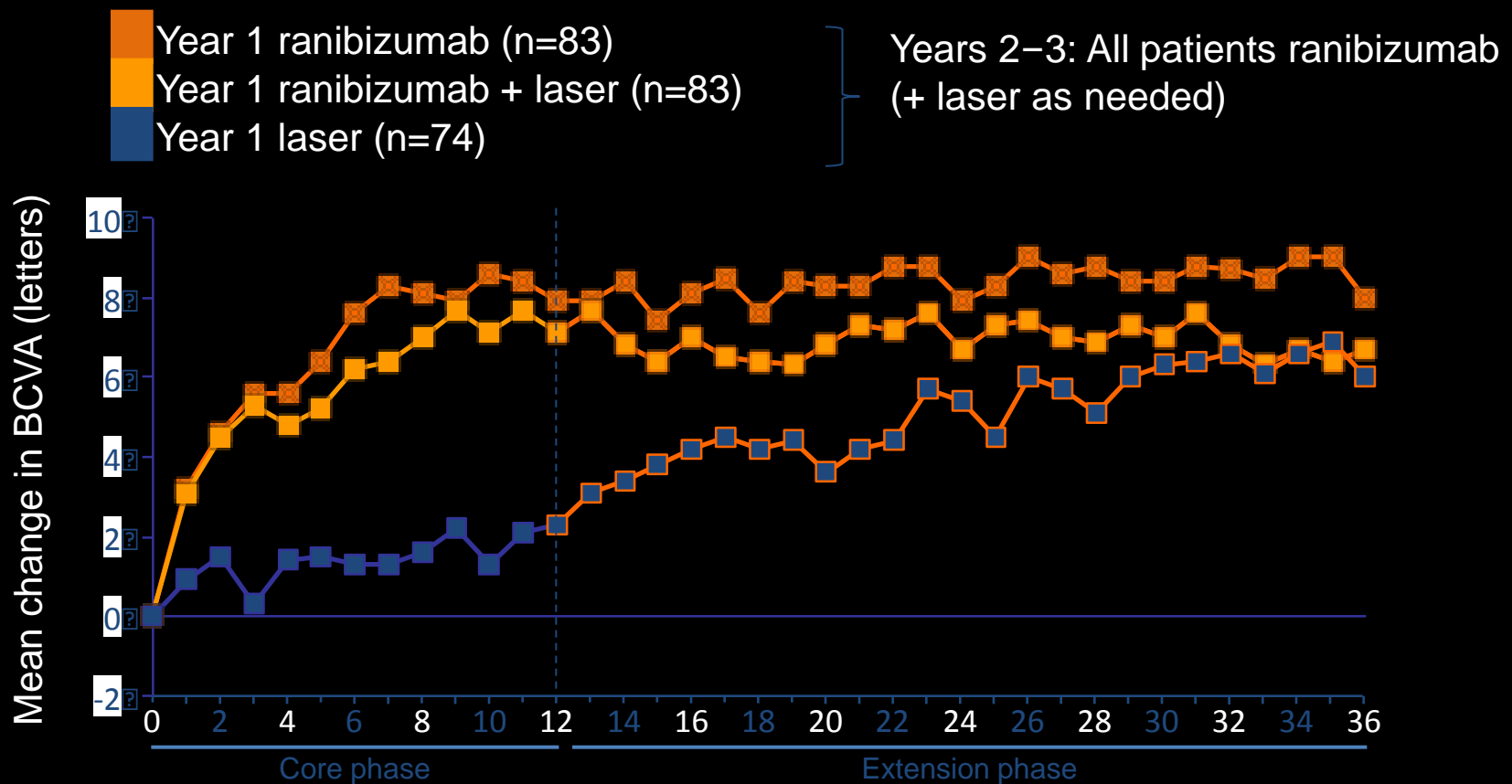
At 2 years, a median 13 avastin injections led to a mean of 8.6 letters gain.

At 2 years, a median of 4 laser treatments led to a mean loss of 0.5 letters ($p < 0.001$).

RESTORE Study extension phase

[Ranibizumab + laser vs. ranibizumab vs. laser in DMO]

Ranibizumab for 3 years resulted in a sustained improvement in BCVA relative to baseline



Chittagong Eye Infirmary And Training Complex, Bangladesh

Cost

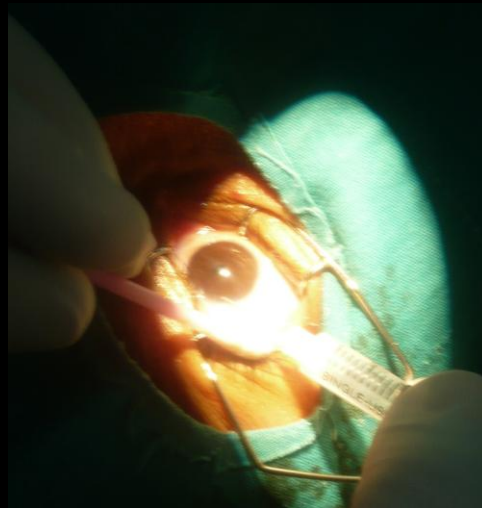
- **CEITC Avastin injection cost BDT 6,000
=\$77 =£50**
- UK drug cost £50
- The very poorest of patients have avastin free of charge

Preparation

- Manufacturer drug prepared in CETIC pharmacy
- Vial=100mg/4ml
Injection=1.25mg/0.05ml
- **Between 60-80 treatments per single vial**
- Storage-cold box and OT fridge



CEITC Avastin Pathway-Operating Theatre



Chittagong, Bangladesh

Capacity

- All treatments in the OT; Retina specialist/Retinal surgeon
- One avastin session per week
- Numbers treated-25 to 45 patients per week
- One Avastin vial/bottle used per week.

Complications/Endophthalmitis

- 1364 injections over 2.75 years, 4.5% total M1 new patients
- 3 cases in last 5 years

Vs. Moorfields Eye Hospital

3 cases 2011/12 (n=9921)

4 cases 2012/13 (n=11503)

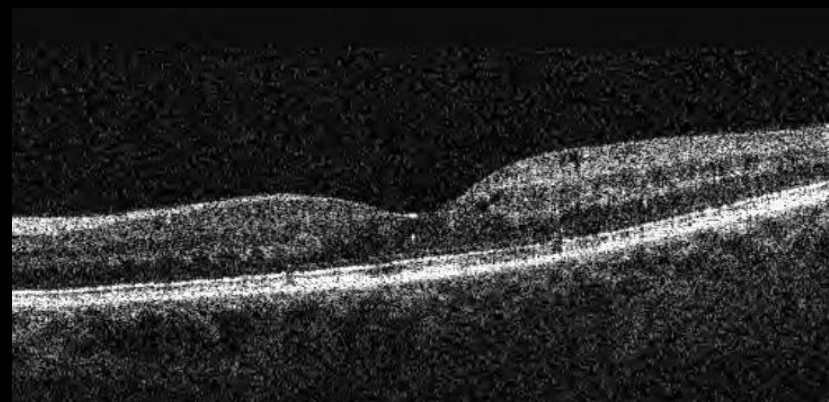
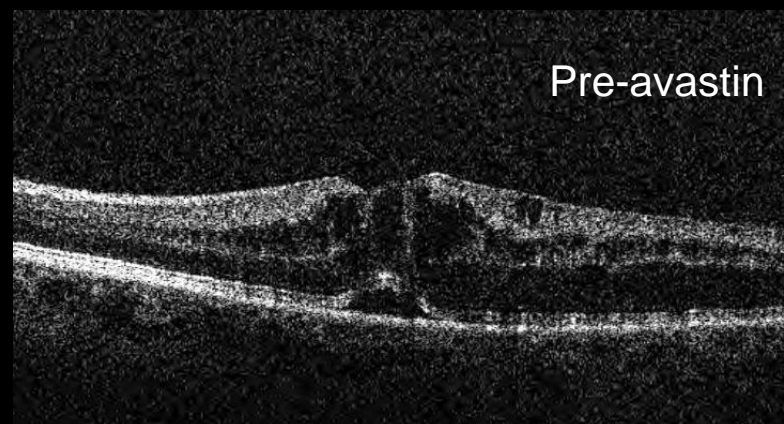
Expected infection rate: 0.5:1000 injections

All conditions including AMD

American Academy of Ophthalmology 2012



- “Review of the available literature indicates that intravitreal injection of anti-VEGF pharmacotherapy is a safe and effective treatment over 2 years for DME”
- Intravitreal anti-VEGF (avastin, lucentis) is first line therapy for DMO.
- Laser no longer first line in USA
- UK: Laser remains an option as first line treatment



4 weeks
post-avastin



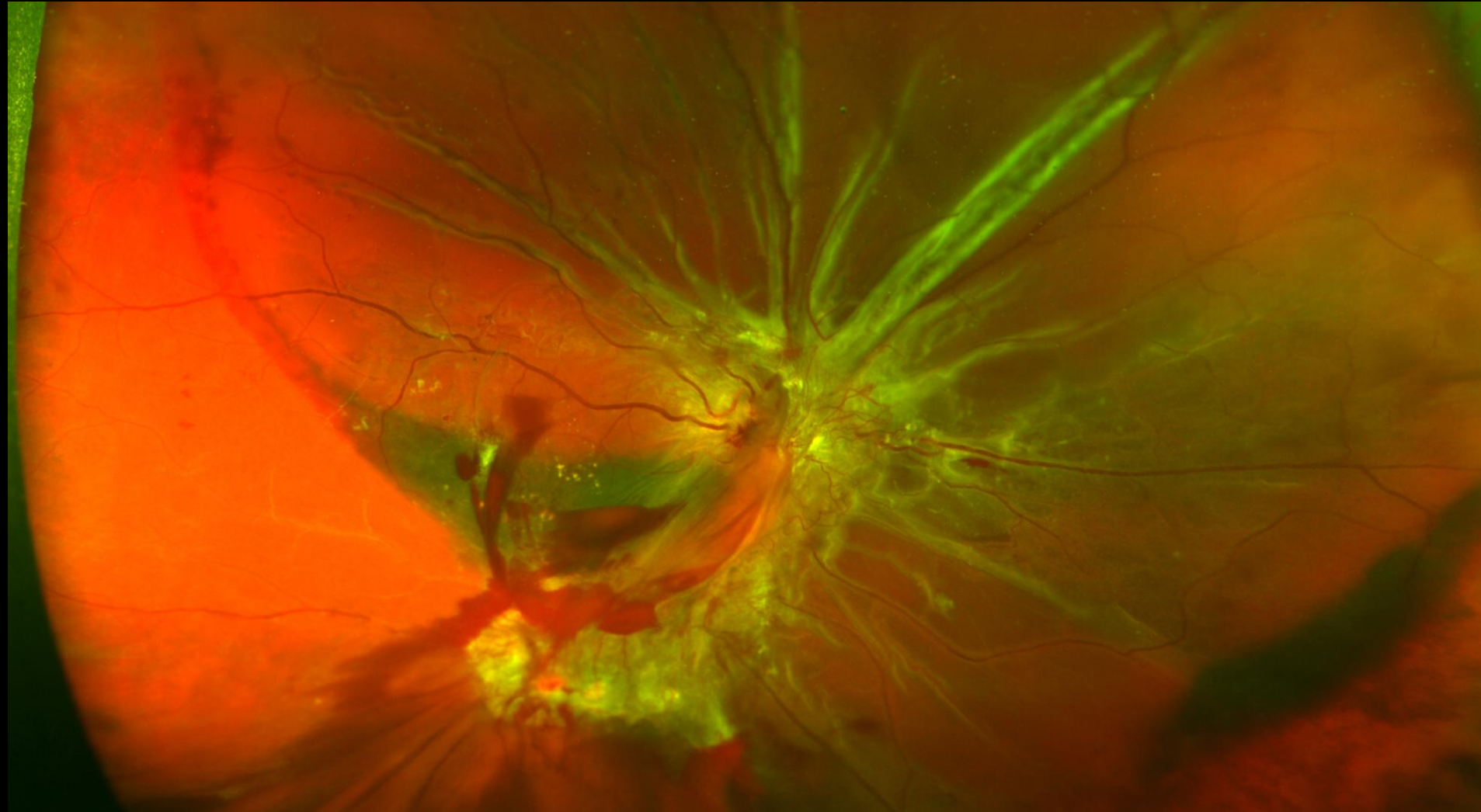
Anti-VEGF for DMO in the UK

- **National Institute for Clinical Excellence (NICE) guidance 2013:**
Supported by the Royal College of Ophthalmologists, UK
- Ranibizumab is recommended as a treatment option for visual impairment due to DMO in adults if:
 - the eye has a central retinal thickness ≥ 400 μm at start of treatment

Note:

Avastin is used in many UK centres for patients that do not meet the NICE criteria

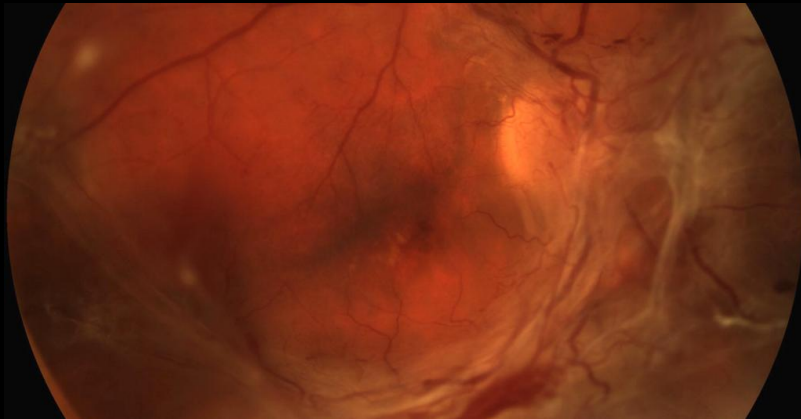
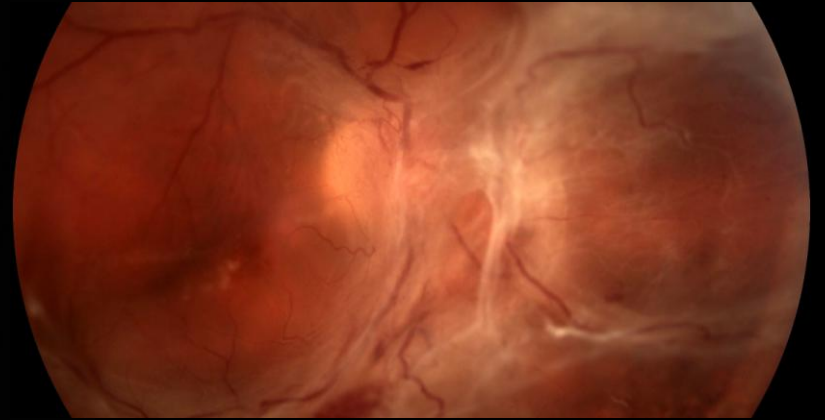
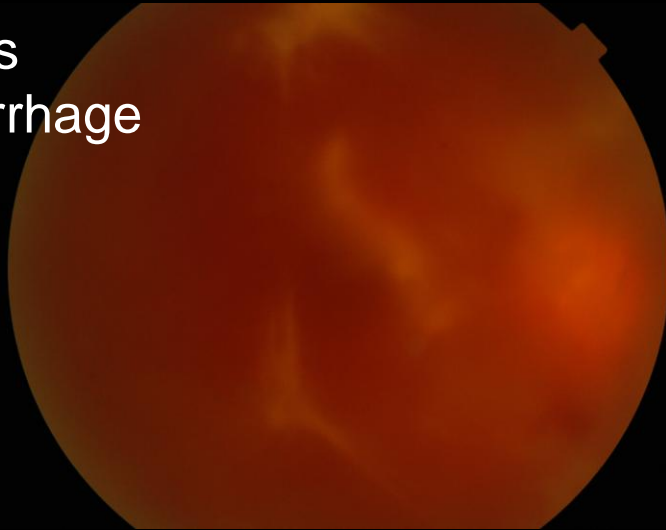
Advanced Proliferative Diabetic Retinopathy with retinal detachment



Risk Factors: Late presentation, Suboptimal laser treatment

Avastin injection before Surgery

Vitreous
haemorrhage



Post-surgery



Discussion



- Development of low-cost intravitreal avastin injection therapy: government & pharma companies
- Develop midlevel healthcare/nurse-led injector services
- Ensure screen-to-treat pathway is comprehensive in resource-poor areas
- Education of anti-VEGF uses and adaptation to operational use

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