

..: CYTOMEGALOVIRUS RETINITIS THE NEGLECTED DISEASE OF THE AIDS PANDEMIC

Cytomegalovirus retinitis is a neglected opportunistic disease, largely undiagnosed and untreated, that claims the sight of thousands of people living with HIV/AIDS in developing countries each year.

“Once you become blind, you have to be taken care of for the rest of your life – it takes away your own independence and that of all your family. It’s catastrophic for everyone.

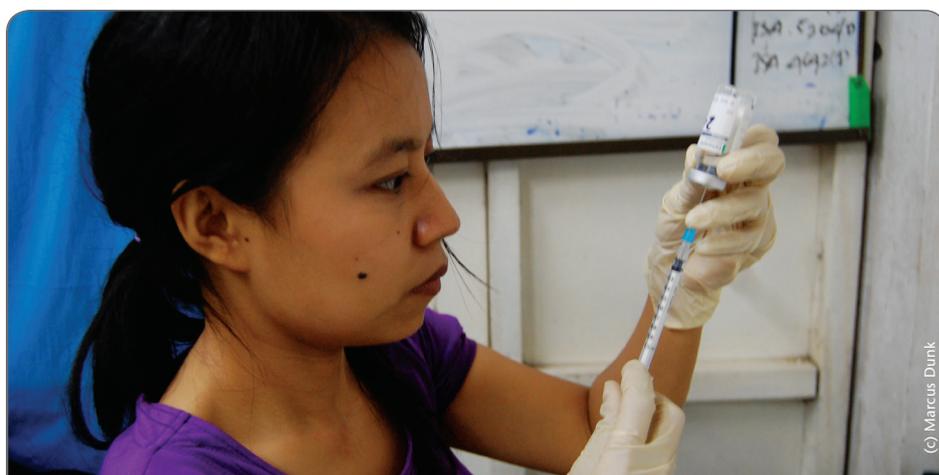
Dr. Karen Kiang, MSF, China, on the impact of a patient’s sight loss due to CMV retinitis. ”

WHAT IS CYTOMEGALOVIRUS RETINITIS?

Cytomegalovirus retinitis (CMVR) is a preventable disease caused by a virus (cytomegalovirus or CMV) that attacks the retina of the eye in patients with suppressed immune systems, specifically those infected with HIV. If untreated, the disease can lead to total and irreversible blindness.

With early detection and treatment of underlying HIV, CMVR can be entirely prevented. However many people in developing countries – particularly those with advanced HIV infection – continue to go undiagnosed and untreated and lose their sight to this disease.

This tragic and unnecessary loss of vision is the result of the absence of evidence-based international and national treatment guidelines for CMV, lack of training in diagnostic techniques and poor access to treatment options.



(c) Marcus Dunk

People are commonly infected with the CMV virus at an early age, but the virus lies latent in the body and only becomes activated once the body’s immune system is severely compromised, for instance by advanced HIV (typically CD4<50). The virus can directly damage the retina

or lead to retinal detachment and, if untreated, the virus can go on to destroy the retina – causing irreversible vision loss. The virus can also attack other organs in the body but in resource-limited settings, CMV disease in other organs may go undiagnosed for lack of access to appropriate tests.



(c) Marcus Dunk

“One day I woke up and it was like a black curtain had gone down over one eye. I tried to rub it away but it wouldn’t go. My mother took me to the hospital and I was put on a course of treatment that meant I had to have injections directly into my eyeball. The doctors told me that if I didn’t start ARV treatment I would go blind. I can’t tell you how terrifying those injections were. I wouldn’t wish them on anybody. After that I agreed to begin ARVs immediately.”

MSF patient on CMVR treatment in Thailand.



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WHO IS AFFECTED BY THE DISEASE?

Before the advent of HIV/AIDS treatment in developed countries, CMV retinitis was a common disease that affected roughly one third of those living with HIV. Now, because of earlier initiation of antiretroviral treatment, it is rarely seen in HIV/AIDS patients in Europe or the US. By bolstering the immune system through antiretroviral therapy, CMV is kept at bay. In low and middle-income countries, despite increased access to ART, a significant proportion of people tend to present for the first time in the late stages of HIV infection and likely for this reason, rates of CMVR have not significantly decreased in these settings.

South and South-East Asia are particularly hard-hit by CMVR. In Asia, approximately 20% of first-presenters for HIV had CD4+ counts less than 100 cells/ μ l¹. In immunosuppressed populations with CD4+ counts below 50 cells/ μ l, CMVR incidence was 3.89/100 patient years². This makes CMV retinitis one of the most common eye diseases seen in patients with HIV/AIDS.¹ As an indication of the scope of the disease, a study in Thailand in 2007 showed that 19% of the cases of bilateral blindness were caused by CMV retinitis, following only after cataracts as the cause of blindness³.



WHY ARE SO FEW PATIENTS DIAGNOSED WITH CMVR?

Currently screening for CMVR among the people most likely to develop the disease – HIV/AIDS patients with very low CD4 counts – is almost non-existent. Screening for CMVR should be part of routine care for those with low CD4+ counts in HIV/AIDS clinics, as it is often asymptomatic, still widely under-diagnosed and is an important cause of preventable blindness. The affected eye can become completely blind within three months.

Furthermore, there is also a 30% likelihood of the contra-lateral eye harboring infection, leading to bilateral visual impairment and increased dependence on family support and health care systems.

Integrating routine examination of the eye in to HIV treatment programmes would be an essential step in increasing case detection early enough to prevent blindness. At the international level, the absence of WHO treatment guidelines continues to contribute to the neglect of this disease in national programmes.

Indirect ophthalmoscopy is the best technique to examine the retina for signs of CMVR and is feasible at the primary care level by HIV clinicians (non-ophthalmologists), but requires some training and follow-up support. Screening based on ocular symptoms has repeatedly proven unreliable⁴.



(C) Marcus Dunk

NEW DIAGNOSTIC OPPORTUNITIES: TRAINING CLINICIANS IN MYANMAR

Many of the challenges in managing CMVR in resource-limited settings derive from the fact that in the absence of access to trained ophthalmologists, few HIV/AIDS clinicians have the skills required to conduct successful ocular screening, diagnosis and intraocular treatment for CMVR. However, the results of a series of training workshops carried out at the request of MSF in Myanmar over a three year period, show that it is feasible to rapidly train HIV/AIDS clinicians in these skills. From 2006 to 2009 ophthalmologists trained 17 clinicians to be able to diagnose CMV retinitis and trained eight health care providers to perform intraocular injections in patients.⁵

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WHAT MEDICATIONS FOR CMV ARE CURRENTLY AVAILABLE?

“ In Myanmar, we have trained our doctors in the effective screening and treatment of CMV retinitis. However, the current treatment is long and uncomfortable. It involves repeated intraocular injections of ganciclovir and has medical risks. An effective oral agent, valganciclovir, exists and avoids the need for injections into the eye, but it remains largely inaccessible due to its high cost.

Dr. Mike Woodman, MSF ”

People living with HIV who are co-infected with CMV will need treatment for both diseases; antiretrovirals to fight HIV and to improve the overall functioning of the immune system so as to control CMV retinitis and fight other potentially fatal illnesses, and in addition a separate treatment to tackle CMV directly.

Current treatment regimens available for CMV retinitis are either prohibitively expensive or else traumatic for patients. The most prevalent current treatment consists of intraocular or intravenous injections with the drug ganciclovir. Intravenous injections present their own logistical challenges, requiring hospitalization of patients and highly trained staff.

Intraocular injections of the drug are highly effective in fighting the virus in the injected eye, but present other challenges; first they don't protect the other eye from infection nor does this technique treat infection in other organs. Second, many patients are frightened at the prospect of the intervention and refuse to go through with it. Those who do go ahead are forced to travel every week to clinic to have their injections, imposing logistical and financial barriers on patients and their families. And finally but perhaps most challenging is the fact that very few clinicians are trained to carry out the intraocular procedure which, as an invasive treatment, brings with it a low rate of serious complications including detachment of the retina.



(c) Joanne Wong

“ The first time I got the injection, I could not even see the doctor as she put the needle in my eye...when I left the clinic the wind was blowing very hard and my eyes felt as if they were going to explode. I just could not hold my tears. I kept having pain for the whole week and before the pain was gone, I had to receive another injection.”

Dou, MSF patient, China



(c) Marcus Dunk

SKY-HIGH PRICES FOR THE BEST TREATMENT OPTION FOR CMVR

For the majority of patients, the best treatment option is with the oral drug, valganciclovir. It is equally effective as intravenous and intraocular ganciclovir and commonly used in high-income countries.^{6,7} Valganciclovir is also able to protect the other eye and other organs from CMVR infection. However, the originator product, Valcyte, from the drug company, Roche, is neither available, nor affordable for the patients

in low-income countries (see Table). One generic manufacturer has marketed its product in India at a high price in the absence of wider generic competition. This situation is due to several factors: the lack of demand for CMVR treatment, existence of patent barriers and also the neglect of donors in prioritizing this opportunistic infection. Sources of quality-assured affordable generic valganciclovir for treating CMVR are urgently needed. Until such alternatives exist, intraocular injections will remain the only available option to treat the disease.

PRICES FOR TREATMENT WITH VALGANCICLOVIR

Offer	Price per tablet in	12 weeks Treatment	27 weeks Treatment
	USD	regimen cost in USD per patient	regimen cost in USD per patient
Roche's Valcyte® price from a procurement agency based in Europe (2012)	10.50*	2,205.93*	4,411.86*
Roche's Valcyte® price in Indian local market (2012)	12.03*	2,526.58*	5,053.16*
Cipla's generic valganciclovir for local Indian market (2012)	3.53*	741.01*	1,482.02*

*These prices are subject to change.

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WHAT NEEDS TO HAPPEN:

CMVR is common, easy to diagnose at an early stage, and treatable. In order to scale-up diagnosis, treatment and management of the disease, and avoid more unnecessary loss of vision, we need:

••• At the international level:

- WHO to rapidly issue evidence-based treatment guidelines and to encourage adoption into national treatment protocols.
- Negotiation with the originator company, Roche, to bring down the price of valganciclovir
- To enable generic competition for quality-assured valganciclovir.

- Donors to include diagnosis and treatment of CMVR infection as a component of the basic HIV model of care.

••• At the national level:

- Decentralised systematic screening for CMVR for all patients with low CD4 count, with or without symptoms, to be integrated into routine care within national HIV programmes at the primary HIV care level.

- Implementation of training schemes for clinicians in indirect ophthalmoscopy so as to integrate CMVR screening into current HIV treatment programmes.
- Scale-up of successful models of diagnosis in resource-limited settings as they have proven to be effective.
- Implementation of training schemes for clinicians to treat CMVR with intraocular injections.



“ Before the procedure, I was so frightened I could feel the worry pressing down on my chest. I’m glad I’ve had it. I used to make jewellery for a living but you need to have good vision for that. I’m hoping that now I’ll be able to go back to it. ”

Myo Oo, MSF patient, Myanmar.

MSF AND CMV RETINITIS

MSF is currently treating 207 patients with CMVR in Myanmar with intraocular ganciclovir. MSF is advocating for better access to oral treatment with valganciclovir for CMVR as this would allow for expansion of the numbers of those we and others could treat and ensure better adherence to treatment.



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