ISSUE BRIEF

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CYTOMEGALOVIRUS RETINITIS: THE NEGLECTED DISEASE OF THE HIV/AIDS PANDEMIC


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Cytomegalovirus retinitis (CMVR) 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.

The absence of systemic screening for the disease among vulnerable populations, coupled with a difficult treatment that involves direct injections into the eye or hospitalisation for intravenous treatment, has excluded many patients from treatment. While there is an oral medicine that could radically improve treatment for both patient and caregiver, patent barriers are currently pricing this treatment out of reach for patients in developing countries, leading to the unnecessary and catastrophic loss of sight in many patients.

> *"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."*
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> **Dr. Karen Kiang, MSF China, on the impact of a patient's sight loss due to CMV retinitis.**

WHAT IS CYTOMEGALOVIRUS RETINITIS?

Cytomegalovirus retinitis is a preventable disease caused by a virus that attacks the retina of the eye in people 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 three key factors: the lack of evidence-based international and national treatment guidelines for CMV; the lack of training in diagnostic techniques; and poor access to treatment options, compounded by the high price of the preferred treatment.


(c) Marcus Dunk

People are commonly infected with CMV at an early age, but the virus lies latent in the body, becoming activated once the body's immune system is severely compromised. 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 profound and irreversible blindness.[1] The virus can also attack other organs in the body, although this may go undiagnosed in resource-limited settings, for lack of access to appropriate tests.

> *"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."*
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> **Person who received treatment for CMVR through MSF in Thailand.**

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WHO IS AFFECTED?

Before the advent of HIV/AIDS treatment in developed countries, CMV retinitis was a common disease that affected roughly one third of people living with HIV. Now, because earlier initiation of antiretroviral treatment (ART) bolsters the immune system, CMVR is kept at bay and therefore rarely seen in people living with HIV/AIDS in wealthy countries anymore. 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 it is most likely for this reason that rates of CMVR have not significantly decreased in these settings.[2]

CMVR IN ASIA

South and Southeast Asia are particularly hard-hit by CMVR. In Asia, approximately 20% of first-presenters for HIV had CD4 counts less than 100.[3] In immuno-suppressed populations with CD4 counts below 50, CMVR incidence was 3.89/100 patient years.[4] 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 cataracts as the cause of blindness.[5]

WHY ARE SO FEW PATIENTS DIAGNOSED?

The lack of WHO guidelines for screening, diagnosis, treatment and care of CMVR continues to contribute to the neglect of this disease in national programmes. Currently, screening for CMVR among people living with HIV/AIDS with very low CD4 counts – the very people most likely to develop the disease – is almost non-existent.

CMVR moves quickly. In Southeast Asia, in a population of patients with advanced HIV, by the time CMVR patients receive an eye evaluation for the first time, 21–36% are already blind.[1] 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 an 11–30% likelihood of the other eye harbouring infection, leading to bilateral visual impairment and increased dependence on family support and health care systems.

Screening based on ocular symptoms has repeatedly proven unreliable.[6] Indirect ophthalmoscopy is the best technique to examine the retina for signs of CMVR and is feasible at the primary care level by non-ophthalmologists (by HIV clinicians, for example), but requires some training and follow-up support.

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.


(c) Marcus Dunk

NEW DIAGNOSTIC OPPORTUNITIES: TRAINING CLINICIANS IN MYANMAR AND THAILAND

Many of the challenges in managing CMVR in resource-limited settings are related to 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 train HIV/AIDS clinicians rapidly 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.[7] Thailand has pioneered the integration of CMVR diagnosis into primary healthcare using telemedicine, whereby digital retinal photographs of patients were evaluated remotely by expert ophthamologists.[1]

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WHAT MEDICATIONS 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 price."

Dr. Mike Woodman, MSF

People living with HIV who are co-infected with CMV need treatment for both diseases: antiretrovirals to control HIV and improve the overall functioning of the immune system, in addition to separate treatment to tackle CMV. Current treatment regimens available for CMVR are either prohibitively expensive or traumatic for patients. Treatment can vary in length – ranging from 12 to 27 weeks. The most prevalent current treatment consists of weekly direct injections into the eye, or intravenous injections with the drug ganciclovir. Intravenous injections present their own logistical challenges, requiring hospitalisation of patients and highly-trained staff.

Intraocular injections of the drug are highly effective in fighting the virus in the infected eye, but present other challenges; first they don't protect the other eye from infection nor do they treat infection in other organs.[1] 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 a clinic to have their injections, imposing logistical and financial barriers on them and their families. And perhaps most challenging is the fact that very few clinicians are trained to carry out the intraocular injections, which, as an invasive treatment, carry a small rate of serious complications, including detachment of the retina.


(c) Joanne Wong

"Since there has not been a decent anti-CMV treatment option available in resource-limited settings for the past 10–20 years – that is treatment that is affordable, palatable, and systemic– most HIV programmes have not implemented screening strategies that would allow for early diagnosis of CMV retinitis. The result has been many cases of unnecessary vision loss and blindness, especially throughout Asia."

Dr. Peter Saranchuk, TB and HIV Adviser, MSF


(c) Marcus Dunk

SKY-HIGH PRICES FOR THE BEST TREATMENT OPTION

For the majority of patients, the best treatment option is the oral drug valganciclovir. It is equally effective as intravenous and intraocular ganciclovir[8,9] and is commonly used in high-income countries to both prevent and treat systemic CMV infection in transplant patients. In addition to the benefit of being an oral medicine that is much easier to administer and to take, valganciclovir is also able to protect the other eye and other organs from CMV infection. However, the originator product, marketed by pharmaceutical company Roche, is neither available nor affordable for people in low-income countries (**see table 1**).

TABLE 1: 2012 PRICES FOR TREATMENT WITH VALGANCICLOVIR

	Price per tablet in US$	12 weeks' treatment cost in US$	27 weeks' treatment cost in US$
Roche price, from a procurement agency based in Europe	$10.50	$2,206	$4,412
Roche price, Indian domestic market	$12.03	$2,527	$5,053
Cipla price, Indian domestic market	$3.53	$741	$1,482

Patents, which can block the production of more affordable generic versions of medicines, are the main cause of the high price of the drug in developing countries. Widespread treatment with valganciclovir will only be possible if more generic manufacturers enter the market and drive down the price through robust generic competition.

In India, the patent on Roche's product was overturned in 2010 following a legal opposition by patient groups and other civil society organisations. As a result, one generic manufacturer has marketed its product in India, but in the absence of wider generic competition and for lack of a greater market, the price still remains relatively high. And the drug cannot be exported for use in other developing countries if Roche has a patent on the drug in those countries.

Furthermore, there is little current incentive for existing and additional generic manufacturers to enter this market because the World Health Organization has not sent a signal that valganciclovir is a priority by putting out an 'Expression of Interest,' which functions as a call to generic manufacturers to produce a given drug. With no Expression of Interest, manufacturers cannot secure WHO quality assurance for their products.

With no WHO quality assurance, and with no Global Fund authorisation to purchase drugs to treat opportunistic infections like CMVR, products are largely ineligible for donor-funded procurement. All of which acts as a barrier preventing generic companies from accessing much wider markets, and in turn preventing countries and organisations from accessing quality-assured generic versions at much more affordable prices.

Sources of quality-assured affordable generic valganciclovir for treating CMVR are urgently needed. Until these are made accessible, intraocular injections or intravenous treatment with ganciclovir will remain the most widely available option to treat the disease. And even access to that treatment is likely to remain limited, given the barriers outlined regarding screening, diagnosis and administration of treatment.

> *"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."*
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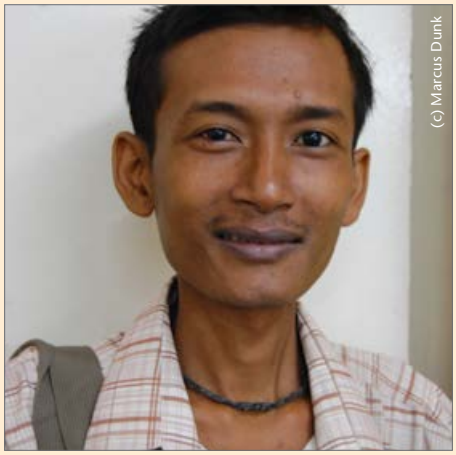
> **Dou, who received CMV treatment through MSF in China.**

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:

> *"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."*
>
> **MyoOo, who received treatment for CMV in Myanmar.**



AT THE INTERNATIONAL LEVEL:

- WHO to rapidly issue evidence-based treatment guidelines and to encourage their adoption into national treatment protocols.
- Negotiation with the originator company, Roche, to bring down the price of valganciclovir.
- Generic competition for quality-assured valganciclovir to ensure the drug is more affordable and more accessible. This will require implementation of TRIPS safeguards and flexibilities by governments, where patent barriers exist, to overcome patent barriers to the production or import of affordable, generic versions of valganciclovir.
- Donors to include diagnosis and treatment of CMVR infection as a component of the basic HIV package of care.

AT THE NATIONAL LEVEL:

- Decentralised systematic screening for CMVR for all patients with low CD4 cell count, with or without symptoms, to be integrated into routine care within national HIV programmes.
- Implementation of training schemes for HIV clinicians in indirect ophthalmoscopy, as well as training in intraocular injections, in order to integrate CMVR screening into current HIV treatment programmes.

MSF AND CMV RETINITIS

MSF is currently treating 225 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 the number of people MSF and others treat to be increased, and ensure better adherence to treatment.

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