Economic evaluation for treatments of cytomegalovirus retinitis in HIV/AIDS patients in Thailand:

Local vs. systemic treatments, unilateral vs. bilateral infection, with vs. without availability of antiretroviral therapy

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Abstract

Purpose: As more effective interventions for treating CMVR through various routes—intravenous (IV), oral (OR), intravitreal injection (IVT) and intraocular implant (IMP) have become available and there are large variations in clinical practice in Thailand, this study is to evaluated the incremental cost-effectiveness ratio (ICER) of providing (1) IVT, (2) IV/OR, and (3) IMP to the patients presenting with CMVR.

Design: This was a model-based analysis for which its input parameters were derived from systematic review of literature, hospital-based survey, and patient's interviews.

Setting: The analysis was under a Thai health care system. However, the model was run using both societal and health care provider's perspective.

Results: IVT was the cheapest treatment option for CMVR and a cost-effective option. Moving from IVT to IV/OR was also cost-effective under a Thai setting since its ICER was less than the recommended threshold by the committee for development of Millennium Development Goals. With the current evidence, offering IMP was cost-ineffective. Providing treatments for the patients with bilateral CMVR was more cost-effective than those with unilateral CMVR as well as offering treatments for the patients with ART was better value for money than treating patients without ART.

Conclusions: IV/OR should be widely recommended for treatment of CMVR in a Thai health care system.

Introduction

Cytomegalovirus retinitis (CMVR) is the most common cause of diseases affecting the eye and the leading cause of blindness among people living with HIV/AIDS (PLWHA) around the world[1]. A significant public health concerns with its ill effects on the short and long-terms quality of life of those infected with the virus[2-4]. The disease typically occurs during the late stages of AIDS, especially, when individuals have a CD4 count less than 50 cells/mm3 and prior to the availability of antiretroviral treatment (ART), it was estimated that one-third of the patients would develop CMVR during their lifetime[1].

Although a free access to ART among PLWHA in industrialised countries have had an enormous impact on its incidence and clinical features[5], many PLWHA in developing counties, who are at risk of CMVR, are not always accessible to ART. In Thailand, the incidence of CMVR is still relatively high, though the universal access of ART has been introduced since 2003. It could be explained that PLWHA may not known their HIV-status and be diagnosed as HIV infection with the occurrence of CMVR. Secondly, CMVR is also be occurred to those who are not candidates for ART (high CD4 level) or those who have recently started or are about to begin taking ART. Thirdly, because of non-adherence to or adverse effects associated with ART and its resistance, many patients will not achieve full immune recovery and therefore are susceptible to the disease.

There are currently many antiviral drugs available for treating CMVR—ganciclovir, foscarnet, cidofovir, and fomivirsen—through various administered routes—intravenous (IV), oral (OR), intravitreal injection (IVT) and intraocular implant (IMP). Once the treatment for CMVR is started, it is likely to be a life unless patients have immune reconstruction (CD4>100 cell/mm3); then they will be able to stop maintenance medications without CMVR progression[6-12].

The challenge for those interested in management of CMVR is to choose between available treatment options. The advantage of systemic treatments—IV, OR, or the mixed between IV for induction phrase and OR for maintenance--is that they are able to prevent CMVR in the other eye if unilateral CMVR has found and also to cure extraocular cytomegalovirus (CMV) infections such as CMV infection of the gastrointestinal system, CMV pneumonitis, CMV neurological disease[1]. However, it has severe complications especially neutropenia which makes those immunocompromise hosts more vulnerable to sepsis and death.

Although local therapeutic options--IVT and IMP, have been proven to be as effective as systematic treatments for treating CMVR, they have no systemic effects and that associated with having CMVR in the other eye in case of presenting with unilateral CMVR, or having extraocular CMV diseases.

In the economic aspect, it may difficult and costly for many patients to receive daily intravenous medication for a two-week course for induction and thereafter on a weekly basis for the maintenance of IV regimen. Even if OR treatment seems to be the most convenience choice, it is less effective than other administrative medications and therefore is not recommended for induction of sight-threatening retinitis[13].

On the other hand, IVT consists of one or two injections each week until the lesions were inactive, which usually take 2-3 weeks, and then maintenance with one injection each 2 weeks continuously, though health care cost for providing IVT is very cheap as a single vial of ganciclovir could be used for treating more than 200 cases of CMVR. It is likely to bring substantial expenses to those patients and their relatives for the travelling since, compared to other health problems, it is more likely that a patient with visual loss needs relative(s) to go with him/her to hospital. In addition, the injection is needed to be twice (one for each eye of the patients) with bilateral CMVR and then have a higher possibility of complications.

In contrast to other strategies, IMP has no daily, weekly or bi-weekly medications. Once ganciclovir implant has been inserted into the vitreous cavity; it is effective for at least six-month duration[14] and, therefore, offers a better quality of life to the patients[15]. However, ganciclovir implant is

expensive and the operation may accompany serious complications e.g. intraocular haemorrhage, endophthalmitis, retinal detachment and malposition of the implant[16]. The implant is only effective for the treated eye, it is important to note the fate of the contralateral CMVR (infection in the other eye) and the occurrence of systemic infections.

We identified four prior economic evaluation studies that investigated value for money for the systematic treatments for CMVR in PLWHA[17-20]. All conducted in the United State and their results are in agreement that IV for induction and OR for maintenance (IV/OR) regimens was superior to IV for both induction and maintenance. However, three studies[17, 18, 20] failed to account for indirect costs or costs associated with adverse effects from the treatments and none of them included local treatment options in the analysis. Three studies [17, 19, 20] did not perform cost-utility analysis which considers important issues relating to quality of life but used intermediate clinical outcomes i.e. day of disease progression free as effectiveness of the treatment, resulted in limitations for making resource allocation decision across health care setting.

Choosing between available treatment options will become even more difficult in developing countries where choice of therapy for any given patient may not be merely selected on the basic of medical factors but also its value for money and not every PLWHA who are eligible for ART will access to the

treatment. In Thailand, for example, there are variations of clinical practices for treating CMVR in PLWHA—some hospitals offer IV/OR, some hospitals provide IVT, and very few of them offer IMP.

Furthermore, there are many issues related to the treatments for CMVR that are not clear at this stage and need to be addressed in this present paper. Because of life expectancy of patients with HIV/AIDS was limited in the past before ART being widely available, a vision lost during a short patient's lifetime could be little affect on overall magnitude of quality adjusted life year (QALY) in the economic evaluation of treatment options for CMVR. Now with the potential longer survival associated with ART, a comprehensive assessment of the treatment options would need to be reviewed.

Importantly, empirical evidences demonstrate that decreased visual acuity in both eyes in a patient was associated with substantial decrease in the utility or preference values compared to the loss of visual acuity in only one eye[21, 22]. We wonder that these findings will affect to the conclusion of previous economic evaluations for CMVR treatment.

Taking into account about above issues, the purposes of this study are to explore: (a) whether offering CMVR treatment to PLWHA is cost-effective in developing countries such as Thailand, (b) which option is the best represent value for money for treating CMVR using both societal and healthcare

provider perspective, (c) whether the treatment that offer the 'best buy' for unilateral CMVR is appropriately for the treatment of bilateral CMVR; and (d) whether patients who have not accessed to ART should be received the same regimen as those who are taking ART.

Design and methods

Over view options

As stated above, the study focuses on three treatment strategies—IV/OR, IVT, and IMP. Ganciclovir is the most popular drug in Thailand due to its long time available in the market and can also be administered via IV, OR, IVT and IMP. In our analysis we applied ganciclovir for three treatment strategies.

IV/OR regimens applied from two multicentre clinical trials[23, 24] which offer 21 days of induction therapy with IV ganciclovir at a dose of 5 mg/kg twice daily for 2 weeks, followed by a dose of 5 mg/kg once daily for a week. The maintenance therapy consists of oral ganciclovir 3,000 mg per day (500 mg x 6 times a day or 1,000 mg x 3 times a day).

IVT regimen is based on the dose of 2 mg (0.1 ml) of ganciclovir weekly intravitreal injection until the lesions were inactive, followed by one injection each 2-4 weeks for the maintenance therapy[25].

IMP strategy is based on US and Brazilian clinical trials[15, 26] for which sustained-release ganciclovir implants was inserted into the vitreal cavity under local anaesthesia. The expected rate of release was 1-2 μg/hour.

Analyses and model

A decision tree validated by a group of experienced ophthalmologists in treating CMVR in PLWHA in Thailand was developed separately for the case of unilateral and bilateral CMVR (**Figure 1 & 2**). Briefly, the models are used to analyse all of the clinically important outcomes and costs of three different strategies. The differences in retinal detachment, endophthalmitis, contralateral CMVR, CMV infection in other organs and catheter related sepsis were used to distinguish among three treatment options.

Figure 1 Decision tree illustrating the probable course of events for the strategies being compared for treating unilateral cytomegalovirus retinitis

E+R = Endophthalmitis and Retinal detachment

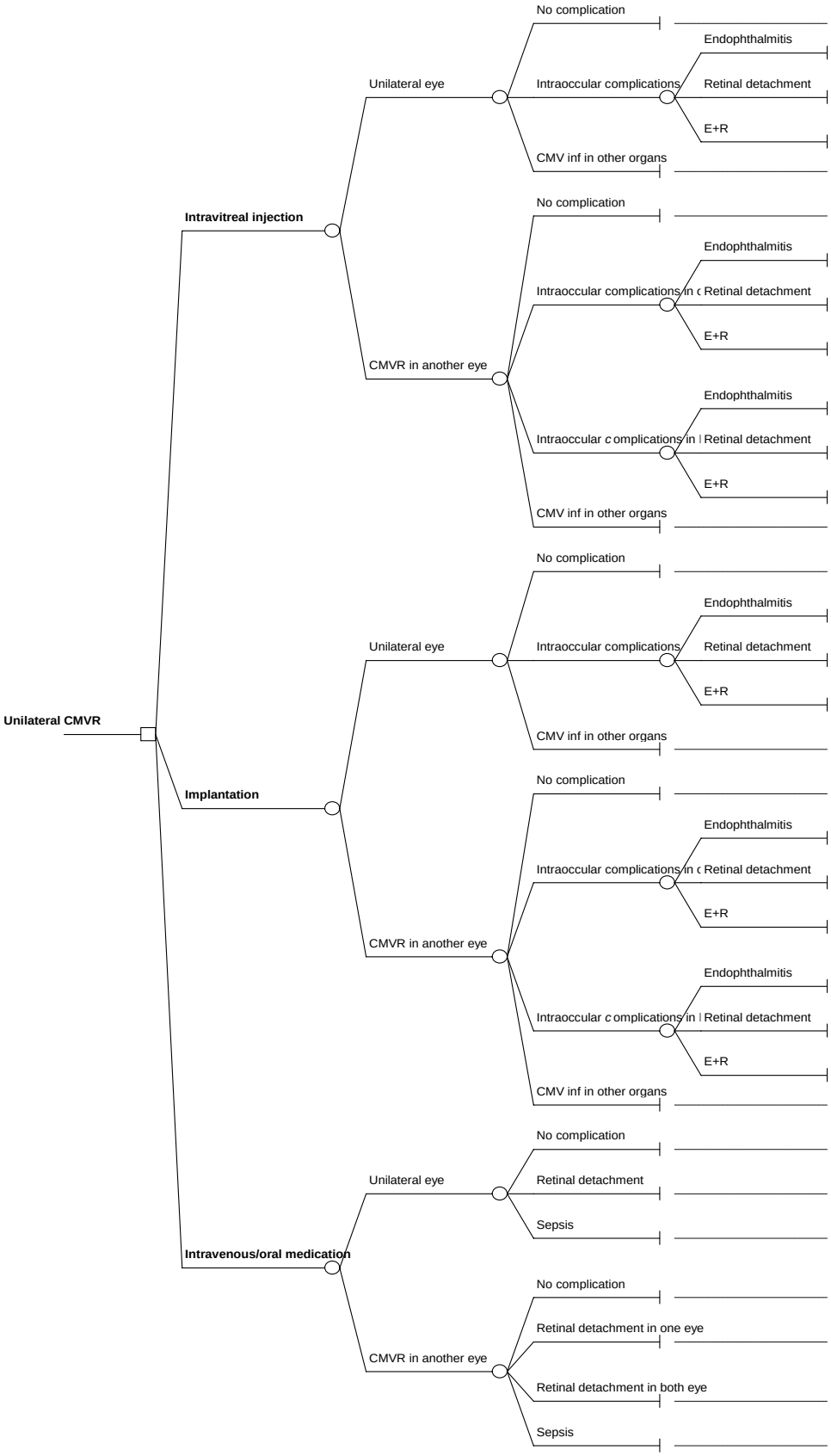
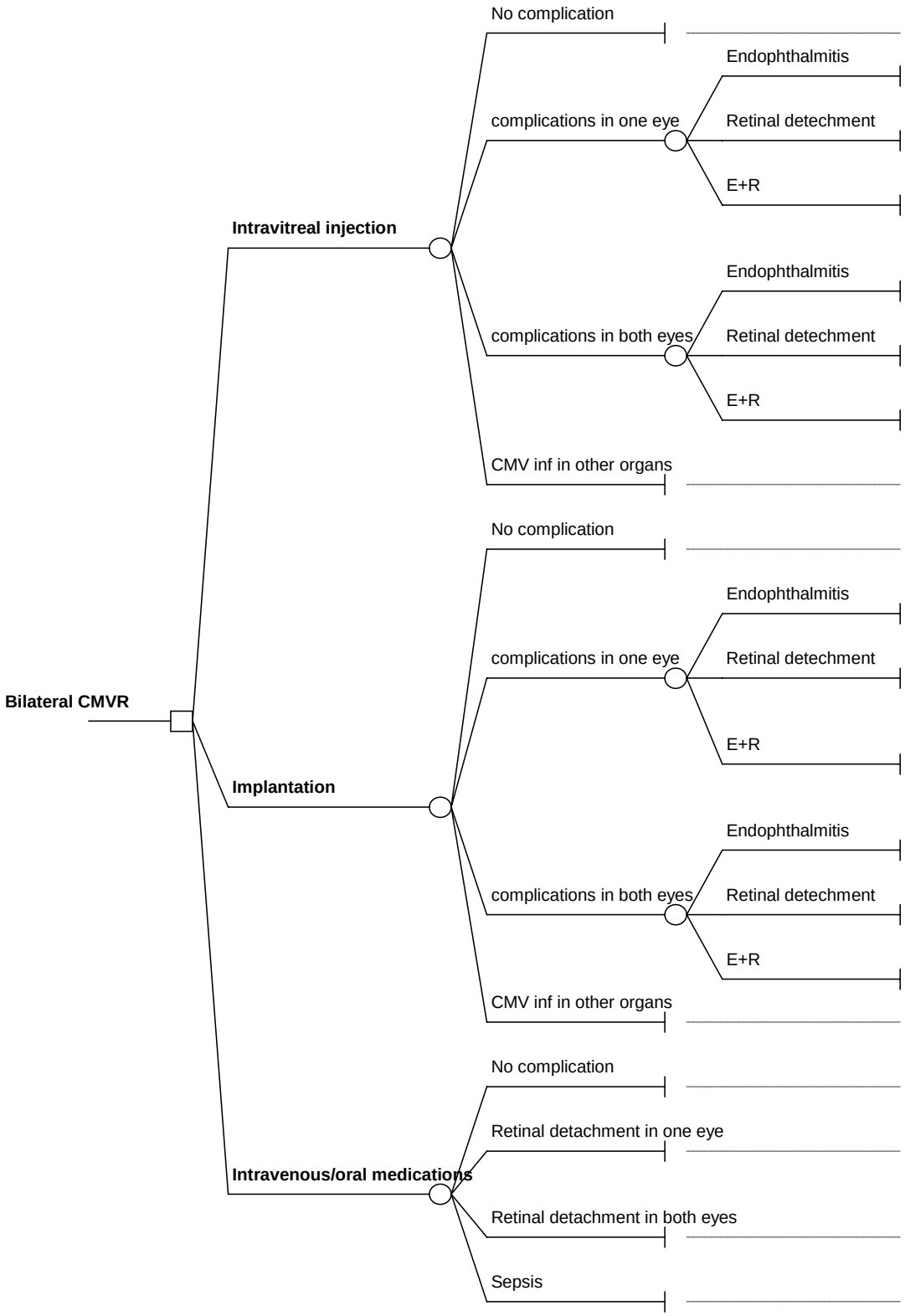


Figure 2 Decision tree illustrating the probable course of events for the strategies being compared for treating bilateral cytomegalovirus retinitis

E+R = Endophthalmitis and Retinal detachment



The models need three types of data; probability data, cost data, and utility estimates for all health states: these data were obtained from a systematic review of literature conducted by two ophthalmologists (KT & SA) using PubMed database searching for publications between 1996 and 2005. A variety of different sources as referenced in **Tables 1**.

Table 1 Model parameters, data sources and values used in the model

Parameters	Mean	SE	Parameter distribution	Ref
Transitional probability variables				
Prob of having contralateral CMVR for local treatments (IVT & IMP)	0.330	0.037	Beta	15,25,26
Prob of having contralateral CMVR for IV/OR ganciclovir	0.198	0.035	Beta	24
Prob of having extraocular CMV infection for local treatments	0.105	0.026	Beta	15,26
Prob of dying from sepsis	0.058	0.018	Beta	27
Prob of achieving a final VA >= 5/200 for treatment of retinal detachment	0.205	0.064	Beta	28
Prob of achieving a final VA >= 5/200 for treatment of endophthalmitis	0.100	0.090	Beta	28
Prob of having intraocular complications for unilateral CMVR with IVT option	0.090	0.020	Beta	25
Prob of having intraocular complications for one eye in bilateral CMVR with IVT option	0.150	0.028	Beta	25
Prob of having intraocular complications for both eyes in bilateral CMVR with IVT option	0.050	0.017	Beta	25
Prob of intraocular complication being endophthalmitis for IVT	0.165	0.085	Dirichlet	25
Prob of intraocular complication being retinal detechment for IVT	0.823	0.088	Dirichlet	25

Parameters	Mean	SE	Parameter distribution	Ref
Prob of intraocular complication being endophthalmitis and retinal detachment for IVT	0.012	0.025	Dirichlet	25
Prob of having intraocular complications for unilateral CMVR with IMP option	0.139	0.023	Beta	15,26
Prob of having intraocular complications for one eye in bilateral CMVR with IMP option	0.139	0.023	Beta	15,26
Prob of having intraocular complications for both eyes in bilateral CMVR with IMP option	0.019	0.019	Beta	15,26
Prob of intraocular complication being endophthalmitis for IMP	0.099	0.054	Dirichlet	15,26
Prob of intraocular complication being retinal detechment for IMP	0.889	0.056	Dirichlet	15,26
Prob of intraocular complication being endophthalmitis and retinal detachment for IMP	0.012	0.020	Dirichlet	15,26
Prob of having retinal detachment for unilateral CMVR with IV/OR regimen	0.133	0.044	Beta	24,29
Prob of having retinal detachment in one eye for bilateral CMVR with IV/OR regimen	0.133	0.034	Beta	24,29
Prob of having retinal detachment in both eyes for bilateral CMVR with IV/OR regimen	0.018	0.013	Beta	24,29
Prob of having sepsis for IV/OR regimen	0.077	0.010	Beta	27
Median survival for patients without ART (years)	6.0	1.5	LogNormal	33-35
Median survival for patients with ART (years)	36.0	12.0	LogNormal	36
Utility parameters				
Baseline utility for patients presenting with unilateral CMVR	0.81	0.05	Beta	Thai cohort & 22
Baseline utility for patients presenting with bilateral CMVR	0.76	0.06	Beta	Thai cohort & 22
Utility for treated patients with unilateral CMVR without complications	0.82	0.04	Beta	Thai cohort & 22

Parameters	Mean	SE	Parameter distribution	Ref
Utility for treated patients with bilateral CMVR without complications	0.74	0.05	Beta	Thai cohort & 22
Temporary utility during IVT treatment	0.65	0.10	Beta	Assumption & 18
Temporary utility during IV/OR treatment	0.75	0.10	Beta	Assumption & 18
Temporary utility during IMP treatment	0.80	0.10	Beta	Assumption & 37
Utility for patients with unilateral endophthalmitis	0.80	0.04	Beta	22, 28
Utility for patients with bilateral endophthalmitis	0.71	0.06	Beta	22, 28
Utility for patients with unilateral retinal detachment	0.68	0.02	Beta	22, 28
Utility for patients with bilateral retinal detachment	0.42	0.13	Beta	22, 28
Cost and resources used parameters				
Unit cost of IVT (per one injection)	192	25	Gamma	Survey
Operation cost for IMP	67,140	13,000	Gamma	39
Maintenance cost for IMP	132	35	Gamma	Survey
Induction cost for IV gancilovir (for a whole course)	31,851	7,502	Gamma	
Maintenance cost for oral ganciclovir per month	552	83	Gamma	Survey
Cost of treatment of endophthalmitis	9,537	9,537	Gamma	Survey, 39
Cost of treatment of retinal detachment	31,488	10,433	Gamma	38
Cost of treatment of CMV inf in other organs	31,850	7,500	Gamma	Survey
Cost of treatment of sepsis	5,500	4,200	Gamma	Survey
Travelling cost (transportation and foods) per visit for patients with unilateral CMVR	556	58	Gamma	Survey
Travelling cost (transportation and foods) per visit for patients with bilateral CMVR	640	401	Gamma	Survey

Parameters	Mean	SE	Parameter distribution	Ref
Average daily income for patient	351	99	Gamma	Survey
Average daily income for relative	369	112	Gamma	Survey
Prob of patients with unilateral CMVR being employed	0.33	0.07	Beta	Survey
Prob of patients with bilateral CMVR being employed	0.30	0.09	Beta	Survey
Average number of relatives visiting hospital with patient with unilateral CMVR	0.67	0.09	Gamma	Survey
Average number of relative visiting hospital with patient with bilateral CMVR	0.83	0.18	Gamma	Survey

CMVR = Cytomegalovirus retinitis

IVT = Intravitreal injection

IV/OR = intravenous injection for induction& oral treatment for maintenance

IMP = intraocular implantation

VA = visual acuity

Outcome measures

A probability of having CMVR in the other eye for local therapies (IVT & IMP) of 0.330 and its standard error (SE)of 0.037 were estimated from meta-analysis of three studies[15, 25, 26] using a Bayesian fixed effect approach. While Kathleen E. Squires[24] reported a probability of developing bilateral CMVR in patients presenting with unilateral CMVR from two clinical trials at 0.198 with SE 0.035.

Only reports from Musch et al[26] and Muccioli & Belfort Jr [15] reported probability of patients developed extraocular CMV disease when they were

treated with IMP (0.105 with SE 0.026). We also applied this figure to the patients treated with IVT in our model.

Throne et al[27] revealed a probability of patients dying from catheter-related complications of 0.058 with SE 0.018. Jabs et al[28] reported visual outcomes of treating retinal detachment among patients with CMVR. We used their figures in our model.

All transition probabilities of having intraocular complications for unilateral and bilateral CMVR treated with IVT were derived from a cohort in Chaingmai university hospital [25]. And the similar parameters used for IMP were drawn from Musch et al and Muccioli & Belfort Jr reports[15, 26]. For IV/OR strategy, probabilities of having retinal detachment for unilateral and bilateral CMVR were modelled from publications made by Drew et al[29] and Squires et al[24] but a probability of having catheter-related sepsis was derived from a paper of Throne et al[27].

Several published studies confirmed that after introducing ART, survival following CMV retinitis increased dramatically[30-33], we reviewed median survival following diagnosis of CMVR and without ART and found its median of 6 months with SE 1.5 [33-35]. Taking into account treatment compliance of treating HIV/AIDS by ART, Lertiendumrong et al [36] reported average mean survival for Thai cohort at 36 months with SE 12.

Utility estimates

From our review, we found only four publications[4, 18, 21, 37] reported about QALY for the patients with CMVR. Unfortunately, there was none of them providing enough information to make complete comparisons among these three treatment strategies. Furthermore, some literatures were not in agreement for the estimated utility scores. Johnson et al[37] reported the difference in preferences(utility) among 80 HIV-infected patients without CMVR in Australia for intravenous ganciclovir (reported median utilities=0.837) compared with oral ganciclovir (reported median utilities=0.475) for maintenance treatment of CMVR. Meanwhile, Griffths et al[18] reported a similar utility score (mean 0.68) for intravenous and oral ganciclovir regimens.

The paper published by Martin et al[21] did not provide comprehensive information of utility data as its intension was to evaluate reliability and validity of a questionnaire for assessing general and disease-specific quality of life among people with CMVR. Although the paper of Kempen et al[4] gave detail methods used for assessment and information about the utility values for patients with newly diagnosed CMVR(mean=63.9, with the use of visual analog scale) and long-standing CMVR(mean=72.3) compared to non-CMVR HIV infected patients(72.5), it did not mention about treatment regimens and that was unable to make direct use in our study.

As we strongly believe that the quality of life for the patients who lost their vision in one eye is much different to those with bilateral visual defects. Hence, our model needed to distinguish utilities between these two. We reviewed and found a paper reported by the submacular surgery trial group[22] demonstrated utility scores based on visual acuity of the worse eye, which can be applied in our study for unilateral CMVR, and the visual acuity in both eyes, which can be used for bilateral CMVR (see **table 2**).

Table 2 Estimated utility scores by visual acuity of the worse eye and both eyes

Visual acuity	**Samples**	**Median**	**SE***
Vision in worse eye			
20/50-20/160	284	0.71	0.02
<=20/200	508	0.65	0.01
Vision in both eyes			
>=20/40 both eyes	9	0.95	0.07
>=20/40 and 20/50-20/160	233	0.74	0.01
>=20/40 and <=20/200	249	0.70	0.02
20/50-20/160 both eyes	51	0.60	0.05
20/50-20/160 and <=20/200	175	0.63	0.02
<=20/200 both eye	84	0.60	0.04
Blind	4	0.30	0.20

Source [22]

We analysed a cohorts of 362 patients receiving IVT in Chiangmai university hospital. The results present in **table 3 and 4** showing visual acuity of CMVR patients presenting with unilateral and bilateral CMVR, both before and after the treatment. From these tables we then estimated utilities for patients with unilateral and bilateral CMVR, before and after the treatment by (see **table 1,** *"utility parameters"*). If there is no definitive treatments available, "Do nothing", we assumed that all infected eyes will lose their sight by 1-3 month.

Table 3 Number of patients presenting with unilateral CMVR by visual acuity pre- and post-treatment by intravitreal injection

Visual acuity	Pre-treatment	Post-treatment
>= 20/40	72	79
20/50-20/160	36	33
<=20/200	95	91
Total	203	203

Source: cohort from Chiangmai university hospital

Table 4 Number of patients presenting with unilateral CMVR by visual acuity pre- and post-treatment by intravitreal injection

Visual acuity	Pre-treatment	Post-treatment
>=20/40 both eyes	30	31
>=20/40 and 20/50-20/160	21	21
>=20/40 and <=20/200	41	22
20/50-20/160 both eyes	11	18
20/50-20/160 and <=20/200	19	23
<=20/200 both eye	37	40

Visual acuity	Pre-treatment	Post-treatment
Blind	0	4
Total	159	159

Source: cohort from Chiangmai university hospital

We assumed the utilities of long-standing treated CMVR patients without complication did not differ among treatment options if they have had immune reconstruction and they have stopped the maintenance therapy. However, as Kempen et al[4] and Jhonson et al[37] reported that the utilities among the newly diagnosed CMVR patients were likely to be affected by treatment options. Empirical evidences[18, 37] demonstrate that IVT should provide worst quality of life during the treatment and IMP should be the best in terms of patient's utility. As Griffths et al[18] offered utility score for intravenous regimen (IV for both induction and maintenance) of 0.68, we used this estimate as a calibre and set the temporary utility during treatment for IV/OR at a higher supposing to be at 0.74 and the temporary utility score for IVT at 0.65. The utility score for IMP should be at the highest since it needs only one operation. As Johnson et al[37] calculated utility score for the oral ganciclovir (for both induction and maintenance) at 0.83, we assumed the utility for IMP should be at a similar level. We finally allocated 0.80 for the temporary utility for IMP. In uncertainty analysis, we assigned a broad SE of 0.1 to all temporary utility scores for each treatment strategies to evaluate the impacts of assumptions made on the utility estimations.

The utilities for complications i.e. endophthalmitis and retinal detachment in one eye and both eyes were derived from a report published by Jabs et al[28]. The report reveals visual outcomes for the patients with complications from CMVR treatment. We applied utility score from table 2[22] and then estimated utility for each type of complications.

Costs

All costs were estimated under Thai setting from reviewed literature[38, 39] and prospective survey by researchers. The costs consisted of (1) direct health care costs i.e. cost of treating CMVR and adverse events, (2) indirect health care costs i.e. travelling costs for patients and their relative(s), and (3) direct non-health care costs i.e. income lost from sick leaves or visiting hospital. All costs shown in table 1 were reported in 2005 Thai Baht. For inter-country comparison, costs can been converted into international dollars using purchasing power parity (PPP) USD exchange rates at 1 USD 2004 = 12.868 Thai Baht[40].

Briefly, we completed micro-cost analysis to estimate medical care costs for providing IVT, IV/OR and IMP from five public hospitals—Chaingmai university hospital, Siriraj hospital, Priest hospital, Chiangkhum hospital and Lumpang hospital. The direct non-medical care cost and direct non-health care cost were collected from 76 patients receiving CMVR treatment at

Chiangmai university hospital and Chingkhum hospital between October and December 2005.

Uncertainty analyses

A probabilistic sensitivity analysis using a second-order Monte Carlo simulation was carried out in Microsoft excel®. All input parameters were assigned a probability distribution to reflect the feasible range of values that each input parameter could attain[41]. To sum up, the beta-distribution was the choice of distribution for probability and utility parameters which were bounded zero-one and the gamma distribution which ensures positive values was modelled for all rate and unit cost parameters.

The simulation then drew one value from each distribution simultaneously and calculated cost and effectiveness pairs. This process was repeated 1,000 times to provide a range of possible values given the specified probability distributions. The cost-effectiveness acceptability curve based on the net benefit approach is also provided to present the relation between the values of the ceiling ratio (willingness to pay for a unit more of QALY) and probability of favouring each treatment strategy.

Results

Using societal perspective, providing the cheapest treatment—IVT, for unilateral CMVR to the patients with and without ART consumed 37,000 and 38,000 Baht and gained 0.21 and 0.22 QALYs respectively (see **table 5**). The incremental cost-effectiveness ratios (ICERs) for moving from 'do nothing' to IVT were 174,000 Baht/QALY for the patients with ART and 173,000 Baht/QALY for the patients without ART.

For the patients with ART, offering IVT for treating bilateral CMVR were slightly more expensive compared to unilateral CMVR but had a significant QALY gained, resulted in a much-improved ICER (46,000 Baht/QALY). Due to a short-life span and, therefore, a small QALYs gained from the patients without ART, ICER of moving from 'do nothing' to IVT for bilateral CMVR was 183,000 Baht/QALY.

The ICERs of moving from the cheapest treatment option (IVT) to the next expensive and the better outcome (IV/OR) were lower (more cost-effective) for the patients with ART compared to the patients without ART, ranging from 121,000 Baht/QALY for bilateral CMVR to 171,000 Baht/QALY for unilateral CMVR. The ICERs for the patients without ART were 435,000 Baht/QALY for unilateral CMVR and 307,000 Baht/QALY for bilateral CMVR.

Table 5 Economic evaluation results using societal perspective

	'Do nothing' to IVT		**IVT to IV/OR**		**IV/OR to IMP**	
Unilateral CMVR	*with ART*	*without ART*	*with ART*	*without ART*	*with ART*	*without ART*
Incremental cost (Baht)*	37,000	38,000	21,000	20,000	20,000	21,000
Incremental QALYs gained	0.21	0.22	0.12	0.05	- 0.04	0.03
Incremental Baht/QALY*	174,000	173,000	171,000	435,000	Dominant	628,000
Bilateral CMVR						
Incremental cost (Baht)*	46,000	48,000	15,000	15,000	55,000	53,000
Incremental QALYs gained	1.01	0.26	0.12	0.05	- 0.01	0.03
Incremental Baht/QALY*	46,000	183,000	121,000	307,000	Dominant	1,584,000

* the numbers were rounded up to nearest 1,000

Moving from IV/OR to the next expensive treatment, IMP, was not always earned more QALYs gained. For the patients with ART, it had slightly decreased the gained for unilateral and bilateral CMVR, resulted in dominant ICERs (more expensive but less effective). However, moving from IV/OR to IMP for the patients without ART gained small health outcomes and theICERs were 628,000 Baht/QALY for unilateral CMVR and 1,584,000 Baht/QALY for bilateral CMVR.

Table 6 shows economic evaluation result from the model using government perspective. When only direct medical care cost was counted, ICERs for moving from 'do nothing' to IVT were improved both for unilateral and bilateral CMVR, and also for the patients treated with ART and without ART. However, due to the more expensive medications for IV/OR regimen and the analysis did not take into account about the saves of indirect medical care cost and non-medical care cost from the regimen, ICERs of moving from IVT to IV/OR for the patients with ART were increased to 264,000 Baht/QALY for unilateral CMVR and 233,000 Baht/QALY for bilateral CMVR, while ICERs for the patients without ART were increased to 639,000 Baht/QALY for unilateral CMVR and 545,000 Baht?QALY for bilateral CMVR.

Table 6 Economic evaluation results using health care provider's perspective

	Do nothing' to IVT		**IVT to IV/OR**		**IV/OR to IMP**	
Unilateral CMVR	*with ART*	*without ART*	*with ART*	*without ART*	*with ART*	*without ART*
Incremental cost (Baht)*	13,000	13,000	31,000	32,000	33,000	32,000
Incremental QALYs gained	0.22	0.22	0.11	0.05	- 0.04	0.03
Incremental Baht/QALY*	57,000	57,000	264,000	639,000	Dominant	932,000
Bilateral CMVR						
Incremental cost (Baht)*	18,000	18,000	26,000	27,000	66,000	66,000
Incremental QALYs gained	1.01	0.26	0.11	0.05	- 0.01	0.03
Incremental Baht/QALY*	18,000	68,000	233,000	545,000	Dominant	1,918,000

* the numbers were rounded up to nearest 1,000

ICERs of moving from IV/OR to IMP for the patients with ART were still dominant as the move was more expensive with less health gained. ICERs for moving from IV/OR to IMP for the patients without ART were 932,000 Baht/QALY for unilateral CMVR and 1918,000 Baht/QALY for bilateral CMVR.

Using societal perspective, **figure 3** reveals cost-effectiveness acceptability curves for the patients with ART which summarise the robustness of the model regarding uncertainty estimation of the programme cost and effect for each treatment strategy. It reveals that if decision makers are willing to pay less than 140,000 Baht/QALY; then IVT was the best option for treating unilateral CMVR since it yielded a higher probability of being cost-effective (the blue thin-line). Also, if they prefer to pay less than 180,000 Baht/QALY; IVT was still the best option for treating bilateral CMVR (the green thick-line). However, if decision makers were willing to pay beyond these thresholds, IV/OR became the better option. It is noteworthy that at any points of the ceiling ratios, ranging from 0 to 900,000 Baht/QALY, IMP was never being the best option for treating both unilateral and bilateral CMVR.

Figure 3 Cost-effectiveness acceptability curves with availability of antiretroviral therapy for patients with CMVR using societal perspective

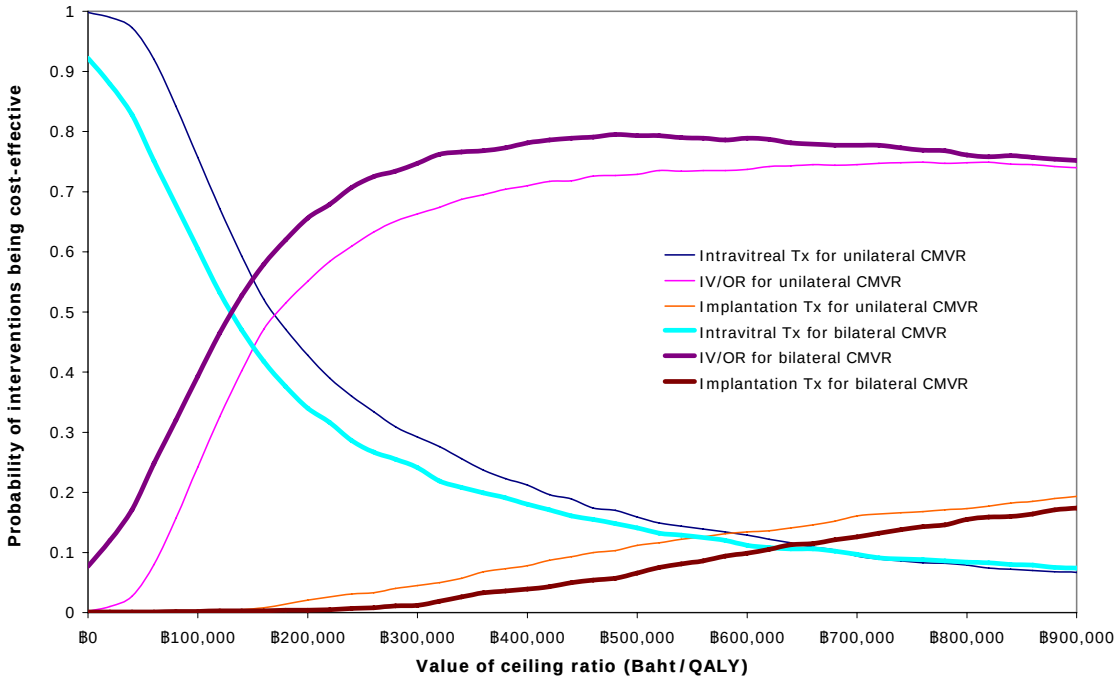


Figure 4 shows results with the use of government perspective. It found that IVT was the best option if decision makers were willing to pay less than 280,000 Baht/QALY for treating unilateral CMVR and 240,000 Baht/QALY for bilateral CMVR.

Figure 4 Cost-effectiveness acceptability curves with availability of antiretroviral therapy for patients with CMVR using government perspective

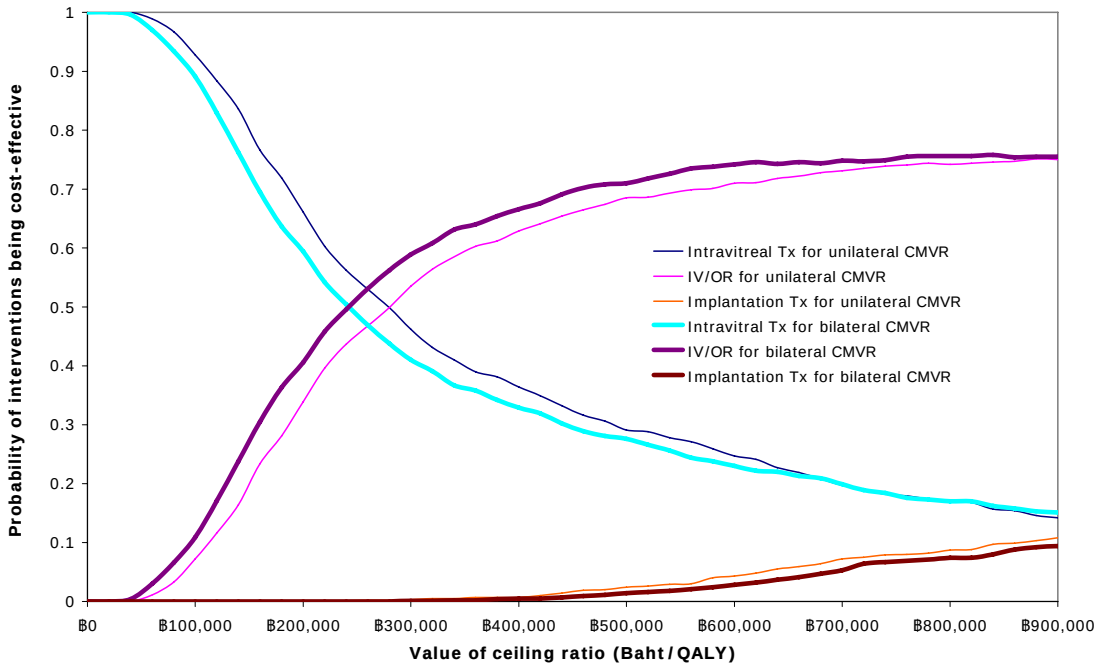
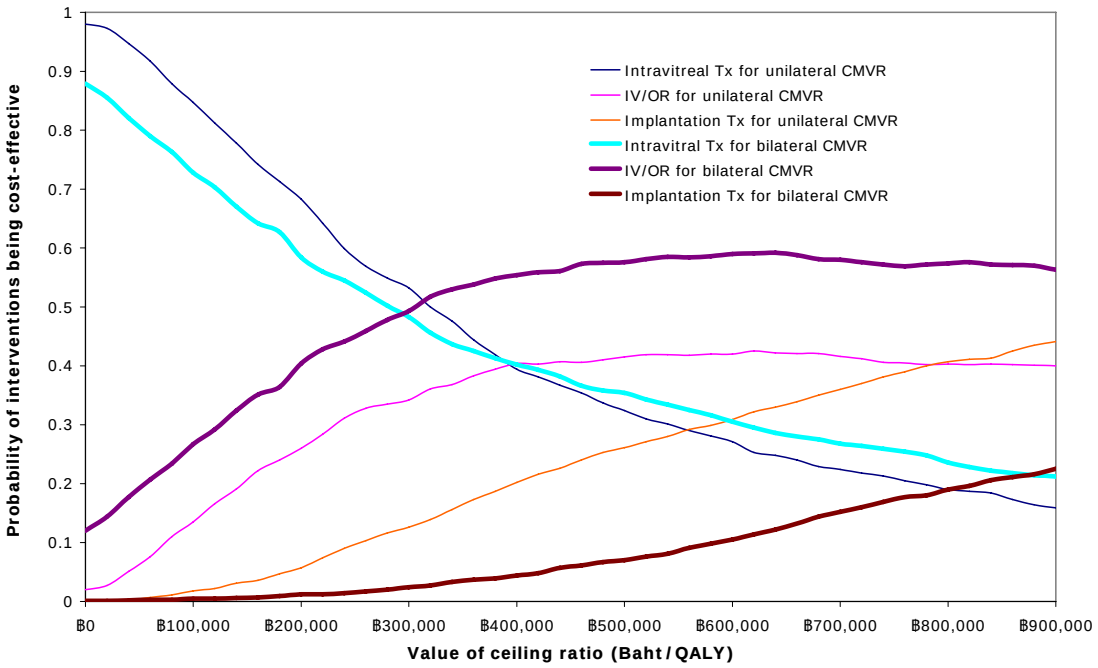


Figure 5 presents cost-effectiveness acceptability curves for the patients without ART using societal perspective. It can be seen that IVT was the best option for treating unilateral CMVR should the societal willingness to pay was less than 400,000 Baht/QALY. IV/OR became the better option if the threshold between 400,000 and 780,000 Baht/QALY and at the threshold beyond 780,000 Baht/QALY IMP was the best option.

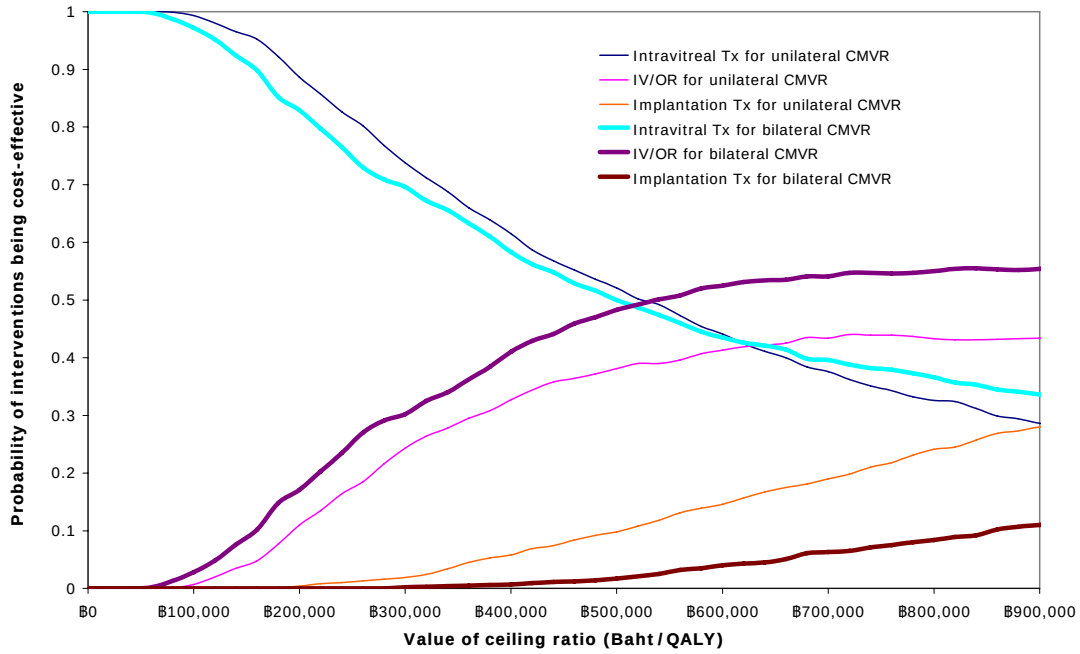
Figure 5 Cost-effectiveness acceptability curves <u>without</u> availability of antiretroviral therapy for patients with CMVR using societal perspective



For treatment of bilateral CMVR, IVT was the best option if the societal willingness to pay was less than 300,000 Baht/QALY and at the threshold beyond that point IV/OR was the best choice.

Lastly, using government perspective for analysis of options for treating CMVR, **figure 6** presents that, at the threshold less than 640,000 Baht/QALY, IVT was the best option for treating unilateral CMVR and if the threshold was as high as 900,000 Baht/QALY, IV/OR and IMP were both the best choice. For treating bilateral CMVR, IVT was the best option as long as the government willingness to pay threshold was less than 520,000 Baht/QALY and, beyond that point, IV/OR was the best option.

Figure 6 Cost-effectiveness acceptability curves without availability of antiretroviral therapy for patients with CMVR using government perspective



Discussions

As many effective interventions for CMVR treatment have evolved and become available over the past decade, the challenge for those interested in management of CMVR is to choose the most appropriate treatment for the patients. The choice is obviously not to be indicated only by medical reasons but also the effective use of limited resources especially in health care system of developing countries such as Thailand[42]. Thus, economic evaluation has been increasingly acceptable as a tool for policy makers in making decisions for allocation of resources in health care.

Although, there is no accepted threshold for adopting health technologies in Thailand[43], the threshold recommend by the committee for development of

Millennium Development Goals for the consideration in developing countries[44] could be used as a proxy in our discussion. The recommendation suggests the use of three times of Gross Domestic Product (GDP) per capital as a threshold and this application would presently lead to a ceiling value in Thailand of 270,000 Baht/QALY[43, 45].

According to the threshold of 270,000 Baht/QALY, the present study indicates that using either the viewpoint of societal or government's, offering IVT for CMVR patients with and without ART represents a good value for money under the Thai setting. In particular, providing IVT for bilateral CMVR to the patients with ART was very cost-effective option (very low ICER).

With availability of ART, our results suggest that moving from IVT to IV/OR is also cost-effective either the societal or healthcare provider's viewpoint is adopted, as their ICERs were all less than the recommended threshold. There are currently large variations in clinical practices for treatment of CMVR in Thailand; thus, IV/OR should be widely recommended to be a treatment of choice for CMVR in the country. It is interesting to note that ICERs for adopting IV/OR using societal viewpoint were lower than that of healthcare provider viewpoint. This can be explained that offering IV/OR would increase expense to the health care providers but, at the same time, save household's healthcare cost.

However, if ART is not available, the study finds that IV/OR is not a preferable choice unless the social willing to pay for one QALY gained at or higher than 300,000-400,000 Baht.

Based on our assessment, it seems that IMP has little role in a Thai setting. Its service is not cost-effective for unilateral and bilateral CMVR, with or without ART for PLWHA.

As stated above that this study is the most comprehensive in assessing value for money for the treatment options for CMVR. It can be used as an example for future economic evaluations for this field (ophthalmology). It demonstrates the possibility and usefulness of doing separate analyses for those with infected one eye and those with infected both eyes. In our study; for example, the differences between ICERs for treatment of unilateral CMVR with IV/OR and ICERs for treatment of bilateral CMVR with IV/OR were almost at 30% for the use of societal perspective and 20% for the use of healthcare provider's perspective, which may influence the decision whether to adopt such technology.

In addition, this study shows that ART has altered a value for money of treating CMVR since ICERs for those patients who have been treated with ART were significantly better than those without ART. The evidences can be explained that among patients treated by ART do not require the additional of

maintenance to prevent relapsing or new CMVR in the other eye or in the other organ systems so that the cost for maintenance therapy was cheaper than those without ART. Also, with the introduction of ART, the patients with CMVR have a much improved survival rate so that they are living longer and the prevention of their loss of vision plays a vital role in the enhancement of ICERs.

There are some limitations regarding to the availability of data used in the model that need to be considered before interpreting our findings. Firstly, the utility values we assigned to the Thai cohort according to their levels of visual acuity were derived from the study that its samples were elders with the median age of 75 years and also the patients were not presenting with CMVR but subfoveal choroidal neovascularisation[22]. However, our estimations were overall inconsistence when we verified them with the previous studies such as ones from Johnson et al[37] and Kempen et al[4].

Secondly, the model applied the same travelling cost and cost for sick-leave for a patient visiting hospital whatever their treatment regimens offered. These assumptions may not be reflect the true costs since some particular treatments are likely to spend a longer time and that need a higher costs paid by patients for undertaking.

Thirdly, the survival for the patients with ART used in our model were from the Thai study which is relatively shorter than other literature[5, 33]. However, the estimation is in agreement with some studies[30, 31]. We believe that the longer survival the better cost-effective ratio for all treatment options will be observed. Lastly, the long-term effects of having ganciclovir implant in the eye are not known and they, therefore, not counted in the analysis.

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Reference

1. Dunn JP, Jabs DA. Cytomegalovirus retinitis in AIDS: natural history, diagnosis, and treatment. AIDS Clin Rev 1995:99-129.

2. Roarty JD, Fisher EJ, Nussbaum JJ. Long-term visual morbidity of cytomegalovirus retinitis in patients with acquired immune deficiency syndrome. Ophthalmology 1993;100:1685-8.

3. Wu AW, Coleson LC, Holbrook J, Jabs DA. Measuring visual function and quality of life in patients with cytomegalovirus retinitis. Development of a questionnaire. Studies of Ocular Complication of AIDS Research Group. Arch Ophthalmol 1996;114:841-7.

4. Kempen JH, Martin BK, Wu AW, Barron B, Thorne JE, Jabs DA. The effect of cytomegalovirus retinitis on the quality of life of patients with AIDS in the era of highly active antiretroviral therapy. Ophthalmology 2003;110:987-95.

5. Kahraman G, Krepler K, Franz C, et al. Seven years of HAART impact on ophthalmic management of HIV-infected patients. Ocular Immunology and Inflammation 2005;13:213-218.

6. Vrabec TR, Baldassano VF, Whitcup SM. Discontinuation of maintenance therapy in patients with quiescent cytomegalovirus retinitis and elevated CD4+ counts. Ophthalmology 1998;105:1259-64.

7. Bertelli D, Stellini R, Cadeo GP. Recurrence of cytomegalovirus retinitis in an HIV-infected patient responsive to highly active antiretroviral therapy late after discontinuation of gancyclovir. Aids 1999;13:1792-4.

8. Whitcup SM, Fortin E, Lindblad AS, et al. Discontinuation of anticytomegalovirus therapy in patients with HIV infection and cytomegalovirus retinitis. Jama-Journal of the American Medical Association 1999;282:1633-1637.

9. Margolis TP. Discontinuation of anticytomegalovirus therapy in patients with HIV infection and cytomegalovirus retinitis. Surv Ophthalmol 2000;44:455.

10. Jouan M, Saves M, Tubiana R, et al. Discontinuation of maintenance therapy for cytomegalovirus retinitis in HIV-infected patients receiving highly active antiretroviral therapy. Aids 2001;15:23-31.

11. Berenguer J, Gonzalez J, Pulido F, et al. Discontinuation of secondary prophylaxis in patients with cytomegalovirus retinitis who have responded to highly active antiretroviral therapy. Clin Infect Dis 2002;34:394-7.

12. Wohl DA, Kendall MA, Owens S, et al. The safety of discontinuation of maintenance therapy for cytomegalovirus (CMV) retinitis and incidence of immune recovery uveitis following potent antiretroviral therapy. HIV Clin Trials 2005;6:136-46.

13. Holland GN. New strategies for the management of AIDS-related CMV retinitis in the era of potent antiretroviral therapy. Ocular Immunology and Inflammation 1999;7:179-188.

14. Palestine AG. Intraocular therapy for cytomegalovirus retinitis. J Int Assoc Physicians AIDS Care 1996;2:25-8.

15. Muccioli C, Belfort R, Jr. Treatment of cytomegalovirus retinitis with an intraocular sustained-release ganciclovir implant. Braz J Med Biol Res 2000;33:779-89.

16. Martin DF, Dunn JP, Davis JL, et al. Use of the ganciclovir implant for the treatment of cytomegalovirus retinitis in the era of potent antiretroviral therapy: Recommendations of the International AIDS Society - USA panel. American Journal of Ophthalmology 1999;127:329-339.

17. Sullivan SD, Mozaffari E, Johnson ES, Wolitz R, Follansbee SE. An economic evaluation of oral compared with intravenous ganciclovir for maintenance treatment of newly diagnosed cytomegalovirus retinitis in AIDS patients. Clin Ther 1996;18:546-58.

18. Griffiths RI, Bleecker GC, Jabs DA, et al. Pharmacoeconomic analysis of 3 treatment strategies for cytomegalovirus retinitis in patients with AIDS. Pharmacoeconomics 1998;13:461-74.

19. Rachlis A, Smaill F, Walker V, Hotchkies L, Jones A. Incremental cost-effectiveness analysis of intravenous ganciclovir versus oral ganciclovir in the maintenance treatment of newly diagnosed cytomegalovirus retinitis in patients with AIDS. Pharmacoeconomics 1999;16:71-84.

20. Lee TA, Sullivan SD, Veenstra DL, et al. Economic evaluation of systemic treatments for cytomegalovirus retinitis in patients with AIDS. Pharmacoeconomics 2001;19:535-50.

21. Martin BK, Gilpin AMK, Jabs DA, Wu AW. Reliability, validity, and responsiveness of general and disease-specific quality of life measures in a

clinical trial for cytomegalovirus retinitis. Journal of Clinical Epidemiology 2001;54:376-386.

22. Submacular Surgery Trials Research Group. Patients' Perceptions of the Value of Current Vision: Assessment of Preference Values Among Patients With Subfoveal Choroidal Neovascularization--The Submacular Surgery Trials Vision Preference Value Scale: SST Report No. 6 10.1001/archopht.122.12.1856. Arch Ophthalmol 2004;122:1856-1867.

23. Drew WL, Ives D, Lalezari JP, et al. Oral Ganciclovir as Maintenance Treatment for Cytomegalovirus Retinitis in Patients with AIDS 10.1056/NEJM199509073331002. N Engl J Med 1995;333:615-620.

24. Squires KE. Oral ganciclovir for cytomegalovirus retinitis in patients with AIDS: results of two randomized studies. Aids 1996;10 Suppl 4:S13-8.

25. Ausayakhun S, Yuvaves P, Ngamtiphakorn S, Prasitsilp J. Treatment of cytomegalovirus retinitis in AIDS patients with intravitreal ganciclovir. J Med Assoc Thai 2005;88:S15-20.

26. Musch DC, Martin DF, Gordon JF, Davis MD, Kuppermann BD. Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. The Ganciclovir Implant Study Group. N Engl J Med 1997;337:83-90.

27. Thorne JE, Jabs DA, Vitale S, Miller T, Dunn JP, Semba RD. Catheter complications in AIDS patients treated for cytomegalovirus retinitis. Aids 1998;12:2321-7.

28. Jabs DA, Enger C, Haller J, de Bustros S. Retinal detachments in patients with cytomegalovirus retinitis. Arch Ophthalmol 1991;109:794-9.

29. Drew WL, Ives D, Lalezari JP, et al. Oral Ganciclovir as Maintenance Treatment for Cytomegalovirus Retinitis in Patients with Aids. New England Journal of Medicine 1995;333:615-620.

30. Walsh JC, Jones CD, Barnes EA, Gazzard BG, Mitchell SM. Increasing survival in AIDS patients with cytomegalovirus retinitis treated with combination antiretroviral therapy including HIV protease inhibitors. Aids 1998;12:613-618.

31. Petruckevitch A, Del Amo J, Phillips AN, et al. Disease progression and survival following specific AIDS-defining conditions: a retrospective cohort study of 2048 HIV-infected persons in London. Aids 1998;12:1007-13.

32. Deayton JR, Wilson P, Sabin CA, et al. Changes in the natural history of cytomegalovirus retinitis following the introduction of highly active antiretroviral therapy. Aids 2000;14:1163-1170.

33. Salzberger B, Hartmann P, Hanses F, et al. Incidence and prognosis of CMV disease in HIV-infected patients before and after introduction of combination antiretroviral therapy. Infection 2005;33:345-349.

34. Cheong I, Flegg PJ, Brettle RP, et al. Cytomegalovirus Disease in Aids - the Edinburgh Experience. International Journal of Std & Aids 1992;3:324-328.

35. Lewis RA, Carr LM, Doyle K, et al. Long-term follow-up of patients with AIDS treated with parenteral cidofovir for cytomegalovirus retinitis: the HPMPC Peripheral Cytomegalovirus Retinitis Trial - The Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. Aids 2000;14:1571-1581.

36. Lertiendumrong J, Yenjitr C, Tangcharoensathien V. Cost and consequence of ART policy in Thailand. Nonthaburi: International Health Policy Program, 2004.

37. Johnson ES, Sullivan SD, Mozaffari E, Langley PC, Bodsworth NJ. A utility assessment of oral and intravenous ganciclovir for the maintenance treatment of AIDS-related cytomegalovirus retinitis. Pharmacoeconomics 1996;10:623-629.

38. Singalavanija A, Sathornsumelee B, Suvette N, Santisuk J. Unit cost of retinal detachment surgery. Thai J Pub Health Ophthalmol 2001;15:131-137.

39. Yenjitr W, Wiriyalapha C, Sribenjarat B, et al. Costs of eye surgery. Thai J Pub Health Ophthalmol 2004;18:35-40.

40. International Monetary Fund. The World Economic Outlook database. Washington, D.C., 2004.

41. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000;17:479-500.

42. Teerawattananon Y, Tangcharoensathien V. Designing a reproductive health services package in the universal health insurance scheme in Thailand: match and mismatch of need, demand and supply. Health Policy Plan 2004;19 Suppl 1:i31-i39.

43. Teerawattananon Y, Vos T, Tangcharoensathien V, Mugford M. Cost-effectiveness of models for prevention of vertical HIV transmission - voluntary counseling and testing and choices of drug regimen. Cost Effectiveness and Resource Allocation 2005;3:7.

44. The commission on macroeconomics and health. Macroeconomics and health: investing in health for economic development. Geneva: World Health Organization, 2001.

45. Teerawattananon Y, Mugford M. Is it worth offering a routine laparoscopic cholecystectomy in developing countries? a Thailand case study. Cost Eff Resour Alloc 2005;3:10.

Reference

1. Dunn JP, Jabs DA. Cytomegalovirus retinitis in AIDS: natural history, diagnosis, and treatment. AIDS Clin Rev 1995:99-129.
2. Roarty JD, Fisher EJ, Nussbaum JJ. Long-term visual morbidity of cytomegalovirus retinitis in patients with acquired immune deficiency syndrome. Ophthalmology 1993;100(11):1685-8.
3. Wu AW, Coleson LC, Holbrook J, Jabs DA. Measuring visual function and quality of life in patients with cytomegalovirus retinitis. Development of a questionnaire. Studies of Ocular Complication of AIDS Research Group. Arch Ophthalmol 1996;114(7):841-7.
4. Kempen JH, Martin BK, Wu AW, Barron B, Thorne JE, Jabs DA. The effect of cytomegalovirus retinitis on the quality of life of patients with AIDS in the era of highly active antiretroviral therapy. Ophthalmology 2003;110(5):987-95.
5. Kahraman G, Krepler K, Franz C, et al. Seven years of HAART impact on ophthalmic management of HIV-infected patients. Ocular Immunology and Inflammation 2005;13(2-3):213-218.
6. Vrabec TR, Baldassano VF, Whitcup SM. Discontinuation of maintenance therapy in patients with quiescent cytomegalovirus retinitis and elevated CD4+ counts. Ophthalmology 1998;105(7):1259-64.
7. Bertelli D, Stellini R, Cadeo GP. Recurrence of cytomegalovirus retinitis in an HIV-infected patient responsive to highly active antiretroviral therapy late after discontinuation of gancyclovir. Aids 1999;13(13):1792-4.
8. Whitcup SM, Fortin E, Lindblad AS, et al. Discontinuation of anticytomegalovirus therapy in patients with HIV infection and cytomegalovirus retinitis. Jama-Journal of the American Medical Association 1999;282(17):1633-1637.

9. Margolis TP. Discontinuation of anticytomegalovirus therapy in patients with HIV infection and cytomegalovirus retinitis. Surv Ophthalmol 2000;44(5):455.

10. Jouan M, Saves M, Tubiana R, et al. Discontinuation of maintenance therapy for cytomegalovirus retinitis in HIV-infected patients receiving highly active antiretroviral therapy. Aids 2001;15(1):23-31.

11. Berenguer J, Gonzalez J, Pulido F, et al. Discontinuation of secondary prophylaxis in patients with cytomegalovirus retinitis who have responded to highly active antiretroviral therapy. Clin Infect Dis 2002;34(3):394-7.

12. Wohl DA, Kendall MA, Owens S, et al. The safety of discontinuation of maintenance therapy for cytomegalovirus (CMV) retinitis and incidence of immune recovery uveitis following potent antiretroviral therapy. HIV Clin Trials 2005;6(3):136-46.

13. Holland GN. New strategies for the management of AIDS-related CMV retinitis in the era of potent antiretroviral therapy. Ocular Immunology and Inflammation 1999;7(3-4):179-188.

14. Palestine AG. Intraocular therapy for cytomegalovirus retinitis. J Int Assoc Physicians AIDS Care 1996;2(5):25-8.

15. Muccioli C, Belfort R, Jr. Treatment of cytomegalovirus retinitis with an intraocular sustained-release ganciclovir implant. Braz J Med Biol Res 2000;33(7):779-89.

16. Martin DF, Dunn JP, Davis JL, et al. Use of the ganciclovir implant for the treatment of cytomegalovirus retinitis in the era of potent antiretroviral therapy: Recommendations of the International AIDS Society - USA panel. American Journal of Ophthalmology 1999;127(3):329-339.

17. Sullivan SD, Mozaffari E, Johnson ES, Wolitz R, Follansbee SE. An economic evaluation of oral compared with intravenous ganciclovir for maintenance treatment of newly diagnosed cytomegalovirus retinitis in AIDS patients. Clin Ther 1996;18(3):546-58.

18. Griffiths RI, Bleecker GC, Jabs DA, et al. Pharmacoeconomic analysis of 3 treatment strategies for cytomegalovirus retinitis in patients with AIDS. Pharmacoeconomics 1998;13(4):461-74.

19. Rachlis A, Smaill F, Walker V, Hotchkies L, Jones A. Incremental cost-effectiveness analysis of intravenous ganciclovir versus oral ganciclovir in the maintenance treatment of newly diagnosed cytomegalovirus retinitis in patients with AIDS. Pharmacoeconomics 1999;16(1):71-84.

20. Lee TA, Sullivan SD, Veenstra DL, et al. Economic evaluation of systemic treatments for cytomegalovirus retinitis in patients with AIDS. Pharmacoeconomics 2001;19(5 Pt 2):535-50.

21. Martin BK, Gilpin AMK, Jabs DA, Wu AW. Reliability, validity, and responsiveness of general and disease-specific quality of life measures in a clinical trial for cytomegalovirus retinitis. Journal of Clinical Epidemiology 2001;54(4):376-386.

22. Submacular Surgery Trials Research Group. Patients' Perceptions of the Value of Current Vision: Assessment of Preference Values Among Patients With Subfoveal Choroidal Neovascularization--The Submacular Surgery Trials. Arch Ophthalmol 2004;122(12):1856-1867.

23. Drew WL, Ives D, Lalezari JP, et al. Oral Ganciclovir as Maintenance Treatment for Cytomegalovirus Retinitis in Patients with AIDS. N Engl J Med 1995;333(10):615-620.

24. Squires KE. Oral ganciclovir for cytomegalovirus retinitis in patients with AIDS: results of two randomized studies. Aids 1996;10 Suppl 4:S13-8.

25. Ausayakhun S, Yuvaves P, Ngamtiphakorn S, Prasitsilp J. Treatment of cytomegalovirus retinitis in AIDS patients with intravitreal ganciclovir. J Med Assoc Thai 2005;88(Suppl 9):S15-20.

26. Musch DC, Martin DF, Gordon JF, Davis MD, Kuppermann BD. Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. The Ganciclovir Implant Study Group. N Engl J Med 1997;337(2):83-90.

27. Thorne JE, Jabs DA, Vitale S, Miller T, Dunn JP, Semba RD. Catheter complications in AIDS patients treated for cytomegalovirus retinitis. Aids 1998;12(17):2321-7.

28. Jabs DA, Enger C, Haller J, de Bustros S. Retinal detachments in patients with cytomegalovirus retinitis. Arch Ophthalmol 1991;109(6):794-9.

29. Drew WL, Ives D, Lalezari JP, et al. Oral Ganciclovir as Maintenance Treatment for Cytomegalovirus Retinitis in Patients with Aids. New England Journal of Medicine 1995;333(10):615-620.

30. Walsh JC, Jones CD, Barnes EA, Gazzard BG, Mitchell SM. Increasing survival in AIDS patients with cytomegalovirus retinitis treated with combination antiretroviral therapy including HIV protease inhibitors. Aids 1998;12(6):613-618.

31. Petruckevitch A, Del Amo J, Phillips AN, et al. Disease progression and survival following specific AIDS-defining conditions: a retrospective cohort study of 2048 HIV-infected persons in London. Aids 1998;12(9):1007-13.

32. Deayton JR, Wilson P, Sabin CA, et al. Changes in the natural history of cytomegalovirus retinitis following the introduction of highly active antiretroviral therapy. Aids 2000;14(9):1163-1170.

33. Salzberger B, Hartmann P, Hanses F, et al. Incidence and prognosis of CMV disease in HIV-infected patients before and after introduction of combination antiretroviral therapy. Infection 2005;33(5-6):345-349.

34. Cheong I, Flegg PJ, Brettle RP, et al. Cytomegalovirus Disease in Aids - the Edinburgh Experience. International Journal of Std & Aids 1992;3(5):324-328.

35. Lewis RA, Carr LM, Doyle K, et al. Long-term follow-up of patients with AIDS treated with parenteral cidofovir for cytomegalovirus retinitis: the HPMPC Peripheral Cytomegalovirus Retinitis Trial - The Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. Aids 2000;14(11):1571-1581.

36. Lertiendumrong J, Yenjitr C, Tangcharoensathien V. Cost and consequence of ART policy in Thailand. Nonthaburi: International Health Policy Program, 2004.

37. Johnson ES, Sullivan SD, Mozaffari E, Langley PC, Bodsworth NJ. A utility assessment of oral and intravenous ganciclovir for the maintenance treatment of AIDS-related cytomegalovirus retinitis. Pharmacoeconomics 1996;10(6):623-629.

38. Singalavanija A, Sathornsumelee B, Suvette N, Santisuk J. Unit cost of retinal detachment surgery. Thai J Pub Health Ophthalmol 2001;15(2):131-137.

39. Yenjitr W, Wiriyalapha C, Sribenjarat B, et al. Costs of eye surgery. Thai J Pub Health Ophthalmol 2004;18(1):35-40.

40. International Monetary Fund. The World Economic Outlook database. Washington, D.C., 2004.

41. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000;17(5):479-500.

42. Teerawattananon Y, Tangcharoensathien V. Designing a reproductive health services package in the universal health insurance scheme in Thailand: match and mismatch of need, demand and supply. Health Policy Plan 2004;19 Suppl 1:i31-i39.

43. Teerawattananon Y, Vos T, Tangcharoensathien V, Mugford M. Cost-effectiveness of models for prevention of vertical HIV transmission - voluntary counseling and testing and choices of drug regimen. Cost Effectiveness and Resource Allocation 2005;3(1):7.

44. The commission on macroeconomics and health. Macroeconomics and health: investing in health for economic development. Geneva: World Health Organization, 2001.

45. Teerawattananon Y, Mugford M. Is it worth offering a routine laparoscopic cholecystectomy in developing countries? a Thailand case study. Cost Eff Resour Alloc 2005;3(1):10.