

## Special Article

# Cytomegalovirus in Solid Organ Transplantation

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**Key words:** Cytomegalovirus (CMV), donor-to-host transmission, ganciclovir, posttransplant infection, valganciclovir, viral infection

**Abbreviations:** CMV, cytomegalovirus; GCV, ganciclovir; NAT, nucleic acid testing; SOT, solid organ transplantation; VGCV, valganciclovir.

## Introduction and Epidemiology

Cytomegalovirus (CMV) is a ubiquitous herpes virus that infects the majority of humans (1). The seroprevalence rates of CMV ranges from 30–97% (2,3). Primary infection manifests as an asymptomatic or self-limited febrile illness in immunocompetent individuals, after which CMV establishes life-long latency in various cells (2,3), which serve as reservoirs for reactivation and as carriers of infection to susceptible individuals (4,5).

CMV is a major cause of morbidity and a preventable cause of mortality in solid organ transplant (SOT) recipients (4). Without a prevention strategy, CMV disease typically occurs during the first 3 months after SOT; this onset has been delayed in SOT patients receiving CMV prophylaxis (6–10). Various terminologies have been used to describe CMV infection and disease in SOT recipients (11,12). To ensure uniformity of reporting in research publications, the following definitions are recommended:

- CMV infection: Presence of CMV replication regardless of symptoms (this should be distinguished from latent CMV). CMV replication is detected (1) nucleic acid testing (NAT; Ref.2), antigen testing and (3) culture. Depending on the method used, CMV infection can be termed as CMV DNAemia or RNAemia (NAT), CMV antigenemia (viral antigen testing) and CMV viremia (culture).
- CMV disease: CMV infection accompanied by clinical signs and symptoms. CMV disease is catego-

rized into (1) CMV syndrome, which manifests as fever and/or malaise, leukopenia or thrombocytopenia, and (2) tissue-invasive CMV disease (e.g. gastrointestinal disease; pneumonitis; hepatitis; nephritis; myocarditis; pancreatitis; retinitis, others). CMV infection without any clinical manifestations should be labeled "asymptomatic CMV infection."

CMV has a predilection to invade the allograft, likely in part due to aberrant immune response within the allograft (13). It also has numerous indirect effects due to its ability to modulate the immune system. CMV has been associated with other infections such as bacteremia (14), invasive fungal disease (15) and Epstein-Barr virus-associated post-transplant lymphoproliferative disease (16). CMV infection is an important contributor to acute and chronic allograft injury (13), including chronic allograft nephropathy (or tubulointerstitial fibrosis in kidney recipients; Ref.17), bronchiolitis obliterans (lung recipients; Ref.18) and coronary vasculopathy (heart recipients; Refs.19,20).

## Risk Factors

CMV disease risk is highest when primary CMV infection occurs in an SOT recipient with no preexisting CMV-specific immunity (21), such as the CMV donor-seropositive, recipient-seronegative (D+R-) patient (5). Other risk factors are the overall state of immunosuppression as determined by the immunosuppressive protocol (e.g. type of drug, dose, timing, duration), host factors (e.g. age, comorbidity, leukopenia and lymphopenia, genetic factors) and others (e.g. cold ischemia time, critical illness, stress; Ref.21). Use of lymphocyte-depleting agents such as antilymphocyte antibodies is associated with CMV disease, particularly when these are used for rejection therapy (22). The risk of CMV disease varies by the transplant type, likely in part due to the amount of lymphoid tissue in transplanted organs and the intensity of immunosuppression. Lung and small intestinal recipients are considered at highest risk among SOT recipients. Coinfections with human herpes virus (HHV)-6 and HHV-7 have been suggested as risk factors (23).

CMV D-/R- SOT recipients have the lowest risk of CMV disease, and they should receive CMV-negative blood or leuko-depleted blood products. The use of mTOR inhibitors (everolimus, sirolimus) is associated with a lower risk of CMV disease (24).

### **Recommendations for CMV risk assessment**

- All donors and transplant candidates should be tested for CMV serology prior to transplantation in order to allow for risk stratification and guide prevention strategies (II-1).
- Serologic test that measures CMV-IgG is recommended (II-1).
  - Unless clinically indicated (i.e. if primary infection is suspected), CMV-IgM measurement is not recommended due to potential for false-positivity (III).
- In patients with borderline or indeterminate CMV serology results, the assignment of serostatus should assume the most conservative approach (III).
  - If a donor CMV serology is borderline or indeterminate, it should be considered as positive (III).
  - If the recipient CMV is borderline or indeterminate, the result should be considered in the context of donor serology to assign the most conservative designation (III). If the donor CMV serology is positive, the recipient will be considered seronegative (i.e. CMV D+/R- mismatch) (III). If the donor CMV serology is negative, the recipient will be considered seropositive.
- Transplant recipients who receive treatment with lymphocyte-depleting drugs, especially if given for the treatment of rejection, should be considered at high risk for CMV disease (II-1).

### **Laboratory Diagnosis**

The laboratory methods to confirm CMV infection are (1) histopathology, (2) culture, (3) serology, (4) antigenemia and (5) molecular assays that detect and quantify CMV nucleic acid (NAT).

Histopathology confirms the presence of tissue-invasive CMV disease. However, this entails an invasive procedure to obtain tissue for diagnosis. Its use has declined due to the availability of non- or less-invasive tests to document CMV infection in the blood (25). However, histopathology is recommended in cases where another concomitant pathology (e.g. graft rejection) or copathogens are suspected, especially when patients do not respond to anti-CMV treatment. Histopathology may be needed when CMV disease is suspected but CMV testing in the blood is negative, such as in some cases of gastrointestinal CMV disease (25). However, repeated histopathology to document clearance of CMV infection in the affected organ, such as the gastrointestinal tract, is generally not clinically necessary (25).

CMV serology to detect CMV-IgM and IgG antibodies has a limited utility for diagnosis of CMV disease after transplantation. Because of immunosuppression, SOT recipients may have delayed or impaired ability to mount an antibody response to CMV infection (26).

Viral culture is highly specific for the diagnosis of CMV infection. However, its use is limited by its modest sensitivity and slow turn-around time (27). Tissue culture may take weeks before the virus can be detected. Shell-vial centrifugation assay has a relatively more rapid turn-around time, but it remains less sensitive compared to molecular assays (27). Nonetheless, culture is still used in isolating CMV in nonblood clinical specimens, partly because molecular methods are not yet optimized for these clinical samples. Viral culture of urine is of low clinical utility in the adult SOT population (see below for its use in pediatric population; Ref.27). Viral culture is needed when phenotypic antiviral drug resistance testing is requested, although genotypic assays are the method of choice for detecting drug resistance (see below; Ref.28–32).

The antigenemia assay is a semiquantitative assay that detects pp65 antigen in CMV-infected peripheral blood leukocytes (27). Antigenemia has higher sensitivity than culture, and is comparable to NAT by polymerase chain reaction (PCR; Ref.27,33). Depending on the number of CMV-infected cells, one can estimate the magnitude of viral replication. The CMV antigenemia assay is useful to guide preemptive therapy, for rapid and sensitive diagnosis of CMV disease, and to guide treatment responses (27). The main disadvantage is the need to process the clinical sample within few hours, and since the test relies on leukocytes, it has limited utility in leukopenic patients (27).

Molecular tests that detect CMV DNA or RNA are the preferred methods for the diagnosis of CMV after SOT (27). Generally, detection of CMV RNA is indicative of active CMV replication. In contrast, detection of CMV DNA may or may not reflect CMV replication since a highly sensitive NAT may amplify latent viral DNA. Hence, quantitative NAT (QNAT) assays have been developed to potentially differentiate active viral replication (typically associated with high viral load) from latent virus (low-level CMV DNAemia if using highly sensitive tests; Ref.27).

Higher CMV load values are generally associated with tissue-invasive disease, while lower values are seen with asymptomatic CMV infection, and intermediate-range viral loads are seen with CMV syndrome; however, there is wide overlap between these categories (34). Higher viral loads are generally observed in CMV D+/R- compared to CMV R+ SOT recipients. The rate of rise in viral load is an equally important marker of CMV disease risk (34–36); the faster the rise in CMV load, the higher is the risk of CMV disease (35,36). There are occasional patients (most often CMV R+ SOT recipients) with tissue-invasive disease (especially late-onset gastrointestinal CMV disease and retinitis) with very low to undetectable viral load in the blood (37); these cases may be due to CMV disease compartmentalization, or the use of less sensitive QNAT assays.

**Table 1:** Characteristics of antiviral prophylaxis and preemptive therapy

	Prophylaxis	Preemptive therapy
Efficacy	Yes: large randomized trials	Yes: smaller trials; fewer D+/R-
Ease	Relatively easy to coordinate	More difficult to coordinate
Late-onset CMV disease	Occurs commonly in CMV D+/R- transplant recipients	Viral load thresholds not standardized Occurs much less commonly
Cost	Higher drug costs	Higher laboratory costs
Toxicity	Greater drug toxicity (myelosuppression)	Potential for less drug toxicity with shorter courses of antivirals
Indirect effects (graft loss, mortality and opportunistic infections)	Positive impact based on meta-analyses and limited comparative trials	Very limited data that preemptive therapy affects indirect effects
Drug resistance	Yes	Yes

QNAT is useful for guiding preemptive therapy, for rapid and sensitive diagnosis of CMV infection, and to guide treatment responses (27). The major drawback to QNAT is the lack of (until recently) an international reference standard (38,39). Accordingly, the viral load results of one assay cannot be directly extrapolated as equal that of another assay (38,40). An up to a 3-log<sub>10</sub> variation among different CMV QNAT has been demonstrated (39), due to differences in assay platform, samples, calibrator standards, gene target, extraction techniques, among others (38).

The lack of standardization in CMV QNAT testing limited the generation and implementation of widely applicable viral thresholds for preemptive therapy, disease prognostication and therapeutic monitoring. Hence, it is recommended that each transplant center should work with their clinical laboratories to define the relevant viral load thresholds for their clinical applications. In 2011, the WHO released the first International Reference Standard for the quantification of CMV nucleic acid, and laboratory and commercially developed CMV QNAT assays should now be calibrated to this standard. This may ensure uniformity in viral load reporting, thereby facilitating to define viral thresholds for various clinical applications (i.e. preemptive therapy, disease prognostication, therapeutic monitoring).

**Recommendations for CMV diagnosis in SOT recipients**

- Viral culture of blood and urine has limited clinical utility for prediction, diagnosis and management of CMV disease in adult patients (II-2).
- Serologic assays to detect CMV-IgM and IgG antibodies should not be used for the diagnosis of CMV disease (III).
- CMV QNAT or pp65 antigenemia should be used for rapid diagnosis of CMV disease (II-2).
- CMV QNAT or pp65 antigenemia should be performed once weekly for monitoring the response of CMV disease to antiviral treatment (II-2).
- CMV QNAT or pp65 antigenemia should be performed once weekly to predict risk of CMV disease, if preemptive therapy is used for CMV prevention (II-2).

- CMV QNAT assays should be calibrated based on the WHO International Reference Standard (III).
  - Studies should report CMV load in IU/mL using QNAT assays that have been calibrated to the WHO International Reference Standard (III).
- Patients suspected to have tissue-invasive CMV disease but with negative QNAT or pp65 antigenemia should have tissue biopsy and histopathology to confirm the clinical suspicion of CMV disease (III).

**Prevention of CMV Disease**

The approaches to CMV prevention in SOT recipients vary among different transplant populations and risk profile. The two major strategies for CMV prevention are: (1) antiviral prophylaxis and (2) preemptive therapy. A comprehensive review of these strategies has recently been published (1).

Antiviral prophylaxis is the administration of antiviral drug to all “at-risk” patients for a defined period after SOT. Preemptive therapy is the administration of antiviral drug only to asymptomatic patients with evidence of early CMV replication in order to prevent CMV disease. For preemptive therapy to be effective, SOT recipients are monitored at regular intervals (usually once weekly) for evidence of early CMV replication using a laboratory assay such as CMV QNAT or pp65 antigenemia. Although most centers employ either of these two major strategies for CMV prevention, others use a hybrid approach wherein short-term antiviral prophylaxis is followed by preemptive therapy during the period of CMV disease risk (41).

Antiviral prophylaxis and preemptive therapy have advantages and disadvantages (Table 1; Ref.21). Preemptive therapy may be associated with lower drug costs and adverse toxicities, but this is offset by the cost of laboratory testing and increased logistic coordination in order to obtain, receive and act upon results in a timely fashion. Preemptive strategy may therefore be a difficult approach for patients who reside at considerable distance from the transplant center. Due to a lack of QNAT standardization (38,39), there is currently no widely acceptable viral load threshold that can guide preemptive therapy. Antiviral

prophylaxis has the advantage of preventing reactivation of other herpes viruses, and has been associated with a lower incidence of indirect CMV effects (42,43). Meta-analyses have demonstrated that antiviral prophylaxis is associated with lower rates of allograft loss and opportunistic infections, and improvement in allograft and patient survival (8,42,43). However, antiviral prophylaxis is associated with late-onset CMV disease, particularly among CMV D+/R- patients (6–9,44). CMV drug resistance has been observed with both strategies (28–31,45,46).

There are only few randomized trials directly comparing preemptive therapy versus antiviral prophylaxis (47–50). These few studies, which were performed mainly in kidney recipients, demonstrate that both are similarly effective for CMV disease prevention. However, long-term graft survival was significantly higher with antiviral prophylaxis (48,49). The conduct of larger multicenter trials to assess the impact of CMV prevention strategies on indirect outcomes is warranted.

### **Antiviral prophylaxis**

Antiviral drugs for CMV prophylaxis are valganciclovir and oral or intravenous ganciclovir. For kidney recipients, valacyclovir is an alternative. In selected patient populations (heart and lung recipients), immunoglobulin preparations are occasionally used as an adjunct in combination with antiviral drugs. Acyclovir should NOT be used for anti-CMV prophylaxis.

The efficacy of ganciclovir, valganciclovir and valacyclovir prophylaxis has been demonstrated in randomized clinical trials (6–9). Among them, valganciclovir is most commonly used for prophylaxis (6,9,51). In a randomized controlled trial of 372 CMV D+/R- kidney, liver, pancreas and heart recipients, CMV disease rate was comparable between patients who received 3 months of oral ganciclovir versus valganciclovir prophylaxis (17.2% valganciclovir vs. 18.4% ganciclovir at 12 months; Ref.6). The improved bioavailability of valganciclovir and its lower pill burden makes it the preferred drug for prophylaxis, even in liver recipients (52). Because of the concern for late-onset CMV disease with 3 months of antiviral prophylaxis in CMV D+/R- patients (6), a trial was performed to compare 200 versus 100 days of valganciclovir prophylaxis (9). In this study of 318 CMV D+/R- kidney recipients, the incidence of CMV disease was 16.1% versus 36.8% in the 200 days versus 100 days groups, respectively (9). Similar studies to assess the optimal duration in liver, heart and pancreas transplant recipients have not been performed, although many centers have already extrapolated these results in the prevention of CMV disease in liver, heart and pancreas recipients.

There are less data on CMV prevention in lung transplant recipients. Previous studies demonstrated that the rates of CMV viremia and disease are high with 3 months or

short courses of antiviral prophylaxis (less than 6 months; Ref.53). Another study reported that the rate of CMV disease was significantly lower with at least 6 months of antiviral prophylaxis (54). In a recent multicenter trial, CMV D+/R- and CMV D+/R+ lung recipients that received 12 months of valganciclovir prophylaxis had significantly lower rates of CMV disease and CMV viremia (4% and 10%) compared to patients who received 3 months of valganciclovir prophylaxis (34% and 64%; Refs.55,56). Others have observed higher rates of CMV disease in CMV D+/R- lung recipients despite 12 months of antiviral prophylaxis, and have adapted an even longer course of antiviral prophylaxis (e.g. anticipated lifelong) in high-risk CMV D+/R- lung recipients (57). However, this was associated with significant myelotoxicity that required temporary or permanent discontinuation of valganciclovir prophylaxis (57). There is currently no good evidence to guide the duration of antiviral prophylaxis in intestinal and composite tissue allograft transplantation.

The efficacy of prophylaxis with either CMV immunoglobulin (CMV-Ig) or intravenous immune globulin (IVIg) in SOT recipients was suggested in a few trials (58,59). A pooled analysis of previous studies suggest that the addition of Ig preparations to antiviral prophylaxis may reduce severe CMV disease and mortality (60), but this finding has been debated (61). Hence, further research is needed to delineate the benefits of Ig preparation as an adjunct to antiviral prophylaxis.

**Late onset CMV disease:** The potential options for the prevention and management of late-onset CMV disease are:

- (1) *Careful clinical follow-up with early treatment of CMV disease when symptoms occur.* SOT recipients (especially CMV D+/R-) should be advised of the risk of CMV disease upon discontinuation of antiviral prophylaxis and that they should immediately seek medical assistance when signs and symptoms of CMV disease occur. Clinicians should have a low threshold for considering CMV disease as a diagnosis in SOT patients presenting with compatible signs and symptoms.
- (2) *Virologic monitoring after completion of antiviral prophylaxis.* Patients who completed antiviral prophylaxis should be monitored using pp65 antigenemia or QNAT periodically for a period of time. However, the optimal duration and frequency of CMV monitoring are not defined. In a few studies, this approach has poor sensitivity and specificity for predicting CMV disease in CMV D+/R- SOT recipients (62,63).
- (3) *Prolong antiviral prophylaxis.* As discussed earlier, extending the duration of antiviral prophylaxis from 3 months to 6 months in CMV D+/R- kidney recipients (9) or 12 months (56) in lung recipients has resulted in further reduction in the incidence of CMV

**Table 2:** Antiviral drugs for CMV prevention and treatment in solid organ transplant recipients

Drug	Treatment <sup>1</sup>	Prophylaxis	Comments on use and toxicity
Valganciclovir	900-mg <sup>2</sup> p.o. twice daily	900 mg <sup>2</sup> p.o. once daily	Ease of administration Leukopenia is major toxicity
Oral Ganciclovir	NOT recommended	1 g p.o. three times daily	Low oral bioavailability High pill burden Leukopenia and risk of resistance development NOT recommended for preemptive therapy
IV Ganciclovir	5-mg/kg IV every 12 h	5 mg/kg IV once daily	Intravenous access and complications Leukopenia is major toxicity
Valacyclovir	NOT recommended	2 g p.o. four times daily	Use in kidney transplant recipients only NOT recommended for heart, liver, pancreas, lung, intestinal and composite tissue transplant recipients High pill burden High risk for neurologic adverse effects NOT recommended for preemptive therapy
Foscarnet	60 mg/kg IV every 8 h (or 90 mg/kg every 12 h)	NOT recommended	Second-line agent for treatment Highly nephrotoxic Used for UL97-mutant ganciclovir-resistant CMV disease NOT recommended for preemptive therapy
Cidofovir	5 mg/kg once weekly × 2 then every 2 weeks thereafter	NOT recommended	Third-line agent Highly nephrotoxic Used for UL97-mutant ganciclovir-resistant CMV disease NOT recommended for preemptive therapy

CMV-immune globulin has been used by some centers as an adjunct to antiviral prophylaxis, especially in heart and lung transplant recipients. The efficacy of this approach is debatable.

The doses of the antiviral drugs are for adults and should be adjusted based on renal function.

<sup>1</sup>These treatment doses are also recommended for preemptive therapy of asymptomatic CMV replication. Foscarnet, valacyclovir, oral ganciclovir and cidofovir are not recommended for preemptive therapy.

<sup>2</sup>Pediatric valganciclovir dose is mg = 7 × BSA × Creatinine clearance.

infection and disease (9,56). Data to support extending the antiviral prophylaxis beyond 3 months in CMV D+/R- liver, heart, and pancreas recipients do not yet exist, but many centers have extrapolated and adapted the clinical practice of prolonging antiviral prophylaxis in these patient groups.

**Specific recommendations for antiviral prophylaxis:**

- Antiviral prophylaxis can be administered to any at-risk SOT recipient to prevent CMV disease after transplantation. The antiviral drugs that can be used for prophylaxis are listed in Table 2. Specific recommendations for various organ recipients are listed in Table 3.
- Valganciclovir is the preferred drug for prophylaxis in adults (level of evidence varies from I-III depending on transplant type). The US FDA has cautioned against valganciclovir prophylaxis in liver recipients due to high rate of tissue-invasive disease compared to oral ganciclovir. However, many experts still recommend its use as prophylaxis in liver recipients (52). Alternative options are intravenous ganciclovir, oral ganciclovir, and for kidney recipients only, valacyclovir. Unselected IVIg and CMV Ig may also be used, but only as an adjunct to antiviral therapy in lung (II-2), heart (II-2) and intestinal (III) transplant recipients.

- In general, antiviral prophylaxis should be started as early as possible, and within the first 10 days after transplantation (I).
- The duration of prophylaxis vary depending on the CMV donor and recipient serologies and the transplant types.
- CMV-specific antiviral prophylaxis is not recommended for CMV D-/R- SOT recipients as long as they receive CMV-negative blood or leuko-depleted blood products (III).

**Preemptive therapy**

With preemptive therapy, SOT patients are monitored weekly for evidence of early CMV replication, which is then treated with valganciclovir or intravenous ganciclovir to prevent its progression to symptomatic disease (64). Preemptive therapy has the potential advantage of targeting antiviral therapy only to the highest risk patients and thereby decreasing drug costs and toxicity. An algorithm for preemptive therapy is depicted in Figure 1.

There is concern regarding the use of preemptive therapy in highest risk CMV D+/R- and lung recipients, due to the potential failure of once weekly surveillance in the face of rapid viral replication (35). Nonetheless, preemptive therapy has been shown to be effective for preventing CMV disease (50).

**Table 3:** Recommendations for CMV prevention in SOT recipients

Organ	Risk category	Recommendation/options (see Table 2 for dose and text for special pediatric issues)	Evidence
Kidney	D+/R-	<i>Antiviral prophylaxis</i> is preferred Drugs: valganciclovir, oral ganciclovir, intravenous ganciclovir or valacyclovir Duration: 6 months <i>Preemptive therapy</i> is an option (see Figure 1). Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg <sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	I
		<i>Antiviral prophylaxis</i> Drugs: Valganciclovir, oral ganciclovir, intravenous ganciclovir or valacyclovir Duration: 3 months <i>Preemptive therapy</i> (see Figure 1). Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg <sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	I
	R+	<i>Antiviral prophylaxis</i> Drugs: Valganciclovir, oral ganciclovir, intravenous ganciclovir or valacyclovir Duration: 3 months <i>Preemptive therapy</i> (see Figure 1). Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg <sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	I
		<i>Antiviral prophylaxis</i> is preferred Drugs: valganciclovir, oral ganciclovir or intravenous ganciclovir Duration: 3–6 months <i>Preemptive therapy</i> is an option (see Figure 1). Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg <sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	I (3-month prophylaxis) III (6-month prophylaxis)
Pancreas and kidney/pancreas	D+/R-	<i>Antiviral prophylaxis</i> Drugs: Valganciclovir, oral ganciclovir or intravenous ganciclovir Duration: 3 months <i>Preemptive therapy</i> (see Figure 1). Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg <sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	I
		<i>Antiviral prophylaxis</i> Drugs: Valganciclovir, oral ganciclovir or intravenous ganciclovir Duration: 3 months <i>Preemptive therapy</i> (see Figure 1). Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg <sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	II-2
	R+	<i>Antiviral prophylaxis</i> Drugs: Valganciclovir, oral ganciclovir or intravenous ganciclovir Duration: 3 months <i>Preemptive therapy</i> (see Figure 1). Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg <sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	I
		<i>Antiviral prophylaxis</i> is preferred: Drugs: valganciclovir (note FDA caution <sup>2</sup> ), oral ganciclovir or intravenous ganciclovir Duration: 3–6 months <i>Preemptive therapy</i> is an option (see Figure 1). Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg <sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	I (3-month prophylaxis) III (6-month prophylaxis)
Liver	D+/R-	<i>Antiviral prophylaxis</i> Drugs: Valganciclovir (note FDA caution <sup>2</sup> ), oral ganciclovir or intravenous ganciclovir Duration: 3 months <i>Preemptive therapy</i> (see Figure 1). Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg <sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	I
		<i>Antiviral prophylaxis</i> Drugs: Valganciclovir (note FDA caution <sup>2</sup> ), oral ganciclovir or intravenous ganciclovir Duration: 3 months <i>Preemptive therapy</i> (see Figure 1). Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg <sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	I
	R+	<i>Antiviral prophylaxis</i> Drugs: Valganciclovir (note FDA caution <sup>2</sup> ), oral ganciclovir or intravenous ganciclovir Duration: 3 months <i>Preemptive therapy</i> (see Figure 1). Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg <sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	I
		<i>Antiviral prophylaxis</i> Drugs: Valganciclovir (note FDA caution <sup>2</sup> ), oral ganciclovir or intravenous ganciclovir Duration: 3 months <i>Preemptive therapy</i> (see Figure 1). Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg <sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	I

Continued

Table 3: Continued

Organ	Risk category	Recommendation/options (see Table 2 for dose and text for special pediatric issues)	Evidence
Heart	D+/R-	<p><i>Antiviral prophylaxis</i> is preferred.</p> <p>Drugs: valganciclovir, oral ganciclovir or intravenous ganciclovir.</p> <p>Some centers add adjunctive CMV immune globulin.</p> <p>Duration: 3–6 months</p> <p><i>Preemptive therapy</i> is an option (see Figure 1).</p> <p>Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg<sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test</p>	<p>I (3-month prophylaxis)</p> <p>III (6-month prophylaxis)</p> <p>II-2 (immune globulin)</p>
	R+	<p><i>Antiviral prophylaxis</i></p> <p>Drugs: Valganciclovir, oral ganciclovir or intravenous ganciclovir.</p> <p>Some centers add adjunctive CMV immune globulin.</p> <p>Duration: 3 months</p> <p><i>Preemptive therapy</i> (see Figure 1).</p> <p>Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg<sup>1</sup> p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test</p>	<p>II-2</p>
Lung, heart–lung	D+/R-	<p><i>Antiviral prophylaxis</i></p> <p>Drugs: valganciclovir or intravenous ganciclovir</p> <p>Duration: 12 months.</p> <p>Some centers prolong prophylaxis beyond 12 months.</p> <p>Some centers add CMV immune globulin.</p>	<p>I (12-month prophylaxis)</p> <p>II-2 (&gt;12 months)</p> <p>II-2 (immune globulin)</p>
	R+	<p><i>Antiviral prophylaxis</i></p> <p>Drugs: valganciclovir or intravenous ganciclovir</p> <p>Duration: 6–12 months</p>	<p>II-2</p>
Intestinal	D+/R-, R+	<p><i>Antiviral prophylaxis</i></p> <p>Drugs: Valganciclovir or intravenous ganciclovir</p> <p>Duration: 3–6 months.</p>	<p>III</p>
Composite tissue allograft	D+/R-, R+	<p><i>Antiviral prophylaxis</i></p> <p>Drugs: valganciclovir or intravenous ganciclovir</p> <p>Duration: 3–6 months.</p>	<p>III</p>

The above recommendations do not represent an exclusive course of action. Several factors may influence the precise nature and duration of prophylaxis or preemptive therapy.

Antiviral prophylaxis should be started as soon as possible, and within 10 days after transplantation. Preemptive therapy is NOT recommended for lung, heart–lung, intestinal and composite tissue allograft transplantation.

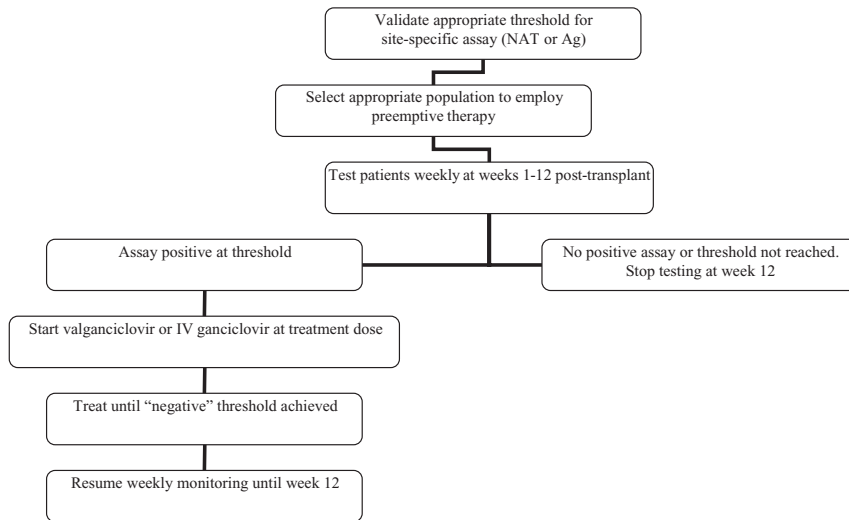
<sup>1</sup>Pediatric valganciclovir Dose is mg = 7 × BSA × Creatinine clearance.

<sup>2</sup>The US FDA has cautioned against valganciclovir prophylaxis in liver recipients due to high rate of tissue-invasive disease compared to oral ganciclovir. However, many experts still recommend its use as prophylaxis in liver recipients. CMV D–/R– SOT recipients do not require anti-CMV prophylaxis. Instead, CMV D–/R– should receive anti-HSV prophylaxis during the early period after transplantation (see chapter on HSV). If blood transfusion is required, CMV D–/R– SOT patients should receive CMV-seronegative or leuko-reduced blood products.

There is debate as to the optimal method for monitoring (pp65 antigenemia or QNAT), the viral load threshold to guide antiviral therapy, the duration of antiviral therapy, and the duration of laboratory monitoring (27). Either pp65 antigenemia or QNAT may be used for monitoring CMV replication (27). However, due to the current lack of standardized assays and reporting (as discussed earlier), site-specific and assay-specific viral load threshold values for initiation of preemptive therapy should be locally validated prior to institution of a preemptive protocol (34). The availability of a WHO CMV International Reference Standard, to which CMV QNAT assays should be calibrated to, should facilitate defining such clinically relevant thresh-

olds. It is likely that such viral load thresholds may be specific for various risk groups, patient populations and immunosuppression-dependent. Clinical research to define these viral thresholds for initiation of preemptive therapy is encouraged.

Once pp65 and QNAT is positive above a defined threshold, treatment with oral valganciclovir (900-mg twice daily) or intravenous ganciclovir (5-mg/kg twice daily) should be initiated. In a clinical trial, viral decay kinetics was similar between valganciclovir and intravenous ganciclovir for preemptive treatment of asymptomatic CMV reactivation (65,66). Since preemptive therapy should treat low-level



**Figure 1: Suggested algorithm for preemptive therapy.** CMV monitoring may be extended beyond 12 weeks in patients who remain severely immunocompromised, as assessed by the clinician.

asymptomatic viremia, experts recommend oral valganciclovir as preferable compared to intravenous ganciclovir for logistic issues.

**Preemptive therapy recommendations:**

- Preemptive therapy is effective for CMV prevention in patients at risk for CMV disease (I).
  - There is ongoing debate on whether preemptive therapy can be highly effective in high-risk populations. Many authorities prefer antiviral prophylaxis for D+/R- and lung transplant recipients while recognizing the clinical utility of preemptive therapy in CMV R+ kidney, liver, pancreas and heart recipients (Table3).
- The laboratory test for CMV monitoring is CMV QNAT or a pp65 antigenemia assay (II-2).
  - The recommended monitoring frequency is once weekly for 12 weeks after transplantation (II-2).
  - The viral load threshold for initiation of preemptive therapy remains center specific in the absence of standardized QNAT reporting system (II-2).
  - Future studies should define the clinically-relevant viral load threshold in IU/mL for the initiation of preemptive therapy (III).
- The recommended antiviral drugs for preemptive therapy are valganciclovir (900 mg twice daily) or intravenous ganciclovir (5 mg/kg every 12 h) (I).
  - Antiviral therapy should be continued until CMV DNAemia or antigenemia is no longer detectable (II-2). Many authorities recommend treating until two consecutive negative weekly pp65 antigenemia or QNAT testing has been attained (III).
  - Laboratory monitoring for CMV by QNAT or pp65 antigenemia is recommended once weekly during antiviral therapy (II-2).
- Further studies are required to determine the efficacy of preemptive therapy versus prophylaxis in reducing the indirect sequelae of CMV (III).

**CMV prevention during ALA therapy and/or treatment of rejection**

The use of lymphocyte-depleting therapy is a major risk factor for CMV disease especially when used for rejection treatment (22,67,68). The administration of intravenous ganciclovir was associated with lower incidence of CMV disease in kidney recipients receiving anti-lymphocyte antibodies (67,68).

**Recommendations for CMV prevention with use of lymphocyte-depleting agents:**

- Antiviral prophylaxis should be given to patients receiving antilymphocyte antibody therapy either as induction or for the treatment of rejection (I).
  - The optimal duration of antiviral prophylaxis is not known, but has been given for 1–3 months (II-2).
  - Options include valganciclovir (900-mg once daily) (III), oral ganciclovir (1-g p.o. thrice daily) (III) or intravenous ganciclovir (5-mg/kg every 24 h) (I).
- Alternative approach to CMV prevention in patients receiving antilymphocyte antibody therapy is a preemptive therapy protocol (III). See Figure 1.
- For patients treated for acute rejection with high-dose steroids, resumption of antiviral prophylaxis or a preemptive strategy may be considered (III).

**Treatment of CMV Disease**

The antiviral drugs for treating CMV disease are intravenous ganciclovir and valganciclovir (Table 2; Ref.66). Oral ganciclovir should NOT be used for treatment of CMV disease because its poor oral bioavailability will lead to insufficient systemic levels. Cautious reduction in the degree of immunosuppression should be considered in SOT patients presenting with CMV disease, especially if the disease is moderate to severe.



The efficacy of intravenous ganciclovir for the treatment of CMV disease has been demonstrated in numerous trials. The duration of therapy varied from 2 to 4 weeks, although recent data suggest that this should be based on clinical and virologic response (66,69,70). Valganciclovir achieves blood levels that are comparable to intravenous ganciclovir treatment, and has been used for the treatment of mild to moderate CMV disease. In a randomized controlled trial that compared 3 weeks of oral valganciclovir to intravenous ganciclovir for the treatment of CMV disease in 321 SOT recipients with mild to moderate CMV disease, both drugs had similar efficacy for the eradication of viremia at 21 days (66). In this study, there were many patients who remained viremic at day 21, suggesting that longer courses of antiviral therapy are needed in many patients (66).

The duration of antiviral therapy should be individualized based on resolution of clinical symptoms and virologic clearance (66,69–71). Generally, SOT recipients with CMV disease should be monitored once weekly using pp65 antigenemia or QNAT to assess virologic response. The risk of CMV relapse is lower among patients with undetectable CMV load at the end of antiviral therapy (69–71). Therefore, patients with CMV disease should remain on full therapeutic dose of antiviral therapy until CMV DNAemia or antigenemia has declined to undetectable levels or negative threshold value for a given test. The duration of treatment is therefore dependent on the sensitivity of the assay being used. An ultrasensitive assay may lead to a more prolonged treatment compared to less-sensitive assays (38,40,72,73). Standardization of CMV QNAT assays should facilitate the derivation of a clinically relevant viral threshold that is safe for discontinuation of antiviral therapy. Further research in this area is encouraged.

### Summary recommendations for treatment of CMV disease

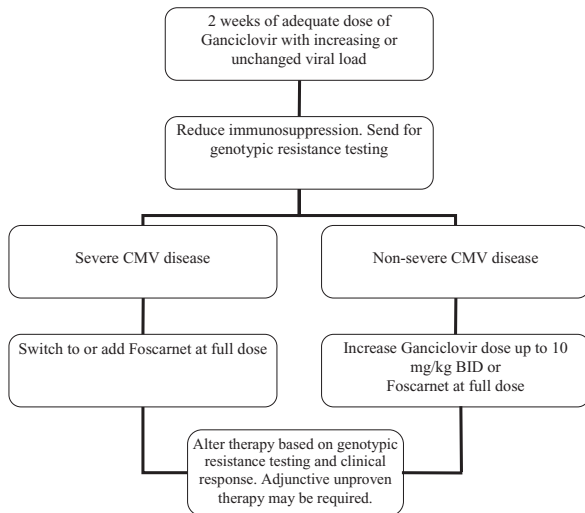
- CMV disease should be treated with intravenous ganciclovir (5 mg/kg every 12 h) (I) or oral valganciclovir (900 mg twice daily) (I).
  - Intravenous ganciclovir is the recommended initial treatment for severe or life-threatening CMV disease, those with high viral load, and those with questionable gastrointestinal absorption (I).
  - Oral valganciclovir is an effective initial therapy for mild to moderate CMV disease (I).
- Treatment of CMV disease should be continued until the following criteria are met (I):
  - Resolution of clinical symptoms, and
  - Virologic clearance below a threshold negative value (test specific; see text) based on laboratory monitoring with CMV QNAT or pp65 antigenemia once a week and
  - Minimum 2 weeks of antiviral treatment.

- Transplant recipients with CMV disease treated initially with intravenous ganciclovir may be switched to oral valganciclovir once there is adequate clinical and virologic control (III).
- Acyclovir and oral ganciclovir should NOT be used for treating CMV disease (II-2). Oral ganciclovir treatment of active CMV replication may lead to emergence of ganciclovir resistance (II-2).
- It is unclear whether addition of IVIg or CMV Ig to existing antiviral treatment regimens has a benefit but may be considered for patients with life-threatening disease, CMV pneumonitis and possibly other severe forms of disease (II-2).
- After completion of full-dose antiviral treatment, a 1–3 month course of secondary prophylaxis may be considered depending on the clinical situation (II-3). Alternatively, patients should have close clinical and/or virologic follow-up after discontinuation of treatment to assess the risk of relapse (II-2).
- Cautious reduction in immunosuppression should be considered in SOT patients presenting with CMV disease, especially if the disease is moderate to severe (II-2).

### Ganciclovir Resistant CMV

Ganciclovir is not active *per se* against CMV unless it has been activated through a process of phosphorylation. The initial phosphorylation of ganciclovir is carried out by a kinase encoded by CMV gene *UL97*. Subsequent phosphorylation by cellular enzymes leads to the active ganciclovir-triphosphate, which competitively inhibits CMV DNA polymerase encoded by the viral gene *UL54*. Therefore, mutations in *UL97* and less commonly in *UL54* can confer ganciclovir resistance (32). The degree of resistance to ganciclovir by CMV *UL97* mutants depends on the site of mutation, which could confer either a low-level or high-level resistance (32). Combined mutations (*UL97* and *UL54*) often have high-level resistance to ganciclovir. Isolated *UL54* mutation (in the absence of *UL97* mutation) is rare (32).

Therapeutic options for ganciclovir-resistant CMV are limited. Because of limited antiviral drugs for treatment, it is highly recommended that the degree of immunosuppression be cautiously reduced. Foscarnet is often the first line for the treatment of *UL97*-mutant ganciclovir-resistant CMV (32). There are only a few studies of foscarnet use in SOT recipients; however, the majority of transplant recipients treated with foscarnet, either alone or in combination with ganciclovir, did improve (29,74–76). The major problem with foscarnet in transplant patients is significant nephrotoxicity (29,74–76). Cidofovir is another alternative for the treatment, although controlled studies in SOT recipients are not available. Cidofovir is highly nephrotoxic (29,74–76). Generally, ganciclovir-resistant CMV isolates with *UL97* mutations remains susceptible to foscarnet and cidofovir. Since ganciclovir, foscarnet and



**Figure 2: Algorithm for treatment of ganciclovir resistance.**

cidofovir act by competitively inhibiting *UL54*-encoded CMV DNA polymerase, mutations in the *UL54* may result in resistance to any or all of these drugs depending on the site of the mutation. Treatment should therefore be guided by genotypic assays (32). Because of the complexity in the management of drug-resistant CMV disease, referral to clinical experts in the field for guidance may be warranted.

The incidence of ganciclovir-resistant CMV remains low (32). It was 1.9% in SOT patients who received 3 months of oral ganciclovir prophylaxis and 0% in patients who received 3 months of valganciclovir prophylaxis (77). The incidence of ganciclovir resistance may theoretically increase with prolonged antiviral administration, however, this was not significantly different between CMV D+/R–kidney recipients who received 3 months compared to 6 months of valganciclovir prophylaxis (28). Certain SOT subpopulations, such as lung transplant recipients, have higher rates of resistance (31,78). Risk factors for resistance include prolonged low-dose oral prophylaxis, D+/R–serostatus, increased intensity of immunosuppression and lung transplantation (79). Resistance has also been demonstrated in patients receiving preemptive therapy, where it was reported in 2.2% of patients (46). Resistance should be suspected if (1) the patient has received prolonged antiviral therapy, either as antiviral prophylaxis or preemptive therapy, (2) the viral load fails to decline or it increases despite 2 weeks of adequate dose antiviral therapy and (3) patients have other risk factors for resistance. Genetic resistance testing should be very helpful in managing resistant CMV. An algorithm for treatment of ganciclovir resistant CMV disease is presented in Figure 2.

Several investigational and off-label drugs have been used for the treating resistant CMV disease. Letermovir (AIC246), which inhibits CMV replication through a specific mechanism that targets viral terminase (80–82), has been

used in a lung transplant recipient with CMV disease that was resistant to treatment with ganciclovir, foscarnet and cidofovir (82). An oral formulation of cidofovir, CMX001, is being investigated for the treatment of ganciclovir-resistant CMV disease (83). Another drug in clinical development is cycloproprvir, which is a DNA polymerase inhibitor with anti-CMV activity (84). Leflunomide and artesunate have been used off-label for treatment of a few cases of drug-resistant CMV disease (85,86). The clinical development of maribavir is uncertain due to disappointing results of clinical trials conducted in bone marrow transplant and liver transplant populations, although it has been used for the treatment of few cases of drug-resistant CMV disease (87). Finally, sirolimus and other mTOR inhibitors have been associated with a lower risk of CMV disease and may be a useful adjunct in the immunosuppressive management of SOT recipients with drug resistant CMV disease.

### **Recommendations for ganciclovir resistant CMV**

- Patients who develop CMV disease after prolonged courses of ganciclovir or valganciclovir administration, either as prophylaxis or preemptive therapy, and those failing to respond to standard ganciclovir treatment should be suspected of having ganciclovir resistant virus. Genotypic testing for resistance should be performed, and this is preferred over phenotypic resistance testing (II-2).
- Immunosuppression should be cautiously reduced in patients with drug-resistant CMV disease (III).
  - Switch to sirolimus-containing regimen may be an option due to the reportedly lower risk of CMV disease in patients receiving mTOR inhibitors (III).
- Options for the empiric treatment of drug-resistant CMV disease include increasing the dose of intravenous ganciclovir (up to 10-mg/kg two times a day) or full-dose foscarnet (see Figure 2) (II-2). Definitive treatment should be guided by the results of genotypic testing (II-2).
  - Other therapeutic options are cidofovir or its new oral formulation that may be available for compassionate release (CMX001), compassionate release letermovir (AIC246), compassionate release maribavir, off-label leflunomide and off-label artesunate (III).
- CMV Ig may be used as adjunct to antiviral drugs (III).

### **Pediatric Issues**

There are only limited data to support definitive recommendations for pediatric transplant populations with regards to CMV prevention and treatment. In addition, other issues such as prevention of EBV-related PTLD may be of primary importance, and may affect the choice of CMV strategies. Overall, proportionately more pediatric patients are at risk of primary and potentially severe CMV disease by virtue of being CMV-seronegative prior to transplantation. Although many donors for pediatric patients

will also be seronegative, the use of living-related or split deceased-donor organs (as in liver transplantation) may result in a marked higher frequency of D+/R- recipients. The following are recommendations specific to pediatric patients:

**Pretransplant screening (pediatrics)**

- Pediatric SOT recipients <18 months of age may have passively acquired maternal antibody, and hence CMV serology may not be reliable. In these patients, CMV culture of urine specimen should be performed (III). If urine CMV culture positive, the recipient is considered infected. If negative, assign the recipient serostatus based on the highest risk level for the purposes of CMV prevention (III). The role of urine CMV QNAT, instead of urine culture, in CMV risk assessment has not been fully investigated. For donors <18 months age, if the CMV serology is positive, the donor should be assumed as truly seropositive (II-2).

**Prevention and treatment (pediatrics)**

The principles and recommendations for the use of antiviral prophylaxis and preemptive therapy in adult recipients are generally applicable to pediatric recipients, with the following qualifying statements.

- Data are limited data regarding the efficacy of preemptive therapy in pediatric patients.
- Data are still limited on the appropriate dose and efficacy of oral ganciclovir and valganciclovir in children. Hence, treatment and prevention strategies continue to be primarily intravenous ganciclovir especially in younger children (II-1). However, oral valganciclovir may be used for prophylaxis and treatment in stable pediatric patients following an initial course of intravenous ganciclovir (III).
- The duration of intravenous ganciclovir treatment is influenced by the risk of catheter-associated bloodstream infections in some settings. The duration of antiviral prophylaxis is also influenced by other factors that vary across centers. These factors include the types of organ transplanted, the institution's experience with CMV disease in their patient population, immunosuppressive practices and the institution's consensus-driven EBV prophylaxis regimen (88) (III).
- There is no single standard of care as this relates to the optimal duration of prophylaxis. The duration of intravenous ganciclovir prophylaxis in major centers varies from a minimum of 14 days to 3 months (II-2).
- Treatment of CMV disease is with intravenous ganciclovir due to a lack of efficacy data of oral therapy in the pediatric population.
- CMV Ig is considered by some experts in combination with intravenous ganciclovir for the treatment of CMV disease in young infants and for treatment of more severe forms of CMV disease (III).

- Intravenous ganciclovir treatment of CMV disease in pediatric SOT recipients may be transitioned to oral valganciclovir in clinically stable patients with well-controlled viremia and clinical symptoms (III).

**Future Research Directions**

There are a number of areas that are being actively explored in basic, translational and clinical research fields related to CMV disease diagnosis, prevention and treatment. An urgent need that can now be realized is the derivation of clinically relevant viral load threshold that should guide risk stratification, preemptive therapy and therapeutic assessments. Clinical and commercial laboratories are encouraged to calibrate CMV QNAT assays based on the recently available WHO International Reference Standard. Studies using calibrated QNAT assays are encouraged to facilitate the derivation of much-needed viral load thresholds.

A number of in-house and some commercially available assays for the assessment of T cell immunity to CMV are being evaluated for their ability to predict the development of CMV disease (89–91). Recent studies have been promising, although more confirmatory tests are needed. It is hoped that these assays will allow better risk-stratification of patients and allow more targeted prevention strategies.

Large clinical trials that will compare antiviral prophylaxis and preemptive therapy remain lacking and should be encouraged in all SOT groups. To attain this, a multicenter collaboration would certainly be needed. An NIH-funded clinical trial comparing antiviral prophylaxis and preemptive therapy has started in five centers in the United States. Recent comparative trials conducted in a modest-sized cohort of kidney recipients demonstrate the potential for antiviral prophylaxis to offer benefits of better long-term allograft survival (47–50).

There are novel preventive and therapeutic options in the horizon. Several CMV vaccine candidates are being tested in early to midphase clinical trials (92). A recent CMV vaccine trial, based on the CMV glycoprotein B with MF59 adjuvant, was found to be highly immunogenic in phase II clinical trials, and was associated with lower rates of antiviral drug use and lesser degree of viremia among vaccines (92). Several novel antiviral drugs are in various stages of clinical development, including letermovir (AIC246), cycloproprvir, maribavir, CMX-001 and others (82,84,87). The successful clinical development of these drugs, some with unique mechanisms of action, will expand the therapeutic armamentarium for the prevention and treatment of CMV in SOT recipients. Finally, studies of CMV prevention and treatment are required for pediatric SOT recipients.

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