phosphonates have proved most valuable and have provided marketed products for HIV (tenofovir, PMPA), HBV (adefovir, PMEA) and CMV (cidofovir, HPMPC) and derivatives of cidofovir (CMX001) are being evaluating clinically for the treatment of poxvirus, polyomavirus and adenovirus infections (reviewed by Lee and Martin[53] and De Clercq[54]). Acyclic nucleoside phosphonates contain an isosteric O–CH_2–P linkage in place of the labile 5′ CH_2–O–P bond.[55] The O–CH_2–P linkage improves the chemical and metabolic stability by making the compounds poor substrates for phosphatases, thereby providing increased stability compared with the typical 5′ –CH_2–O–P bond. This increased stability, in turn, provides for long intracellular half-lives and persistent antiviral effects.[56,57] In addition, the intrinsic phosphonate allows bypass of the first phosphorylation step required for activation of nucleotide analog during anabolic phosphorylation to the diphosphate form. However, the high polarity of the phosphonate often necessitates development of a prodrug for optimal delivery (membrane permeability).

CDV is currently licensed for the treatment of human cytomegalovirus retinitis and is administered as a topical ophthalmic solution. Topical application of CDV has been used to treat molluscum contagiosum, a cutaneous skin disease caused by molluscum contagiosum virus, a poxvirus related to OPVs.[58] CDV exhibits antiviral activity against adenoviruses, herpesviruses, iridoviruses, polyomaviruses, hepadnavirus, papillomavirus and poxviruses in viral replication assays in cell culture (reviewed by De Clercq *et al.*[59]). CDV is active against a spectrum of OPV, including variola virus (Table 4.2), and the synthesis of CDV is outlined in Figure 4.2.

Table 4.2 Antiviral activity of CMX001, CDV and ST-246.

		EC_{50} (μM)			
Viral class	*Virus*	*CMX001*	*CDV*	*ST-246*	*Ref.*
Orthopoxvirus	VARV	0.1	27.3	0.05	50, 51
	MPXV	0.07	4.6	0.01	50, 51
	CTGV	N.D.[a]	7.7	0.001[b]	117
	VACV	0.8	46	0.01	51, 75
	CPXV	0.5	42	0.05	51, 118
	RPXV	0.5	39	N.D.	50
	ECTV	0.5	12	0.07	42, 51
Herpesvirus	HSV-1	0.06	15	>40	50, 51
	CMV	0.0009	0.38	>40	50, 51
	HHV 6	0.004	0.2	N.D.	50
	VZV	0.0004	0.5		
	EBV	0.04	>170		
Adenovirus	AdV 5	0.02	1.3		
Papillomavirus	HPV	17	200		
Polyomavirus	BKV	0.13	115.1		
	JCV	0.045	N.D.		

[a]N.D.: not determined.
[b]EC_{50} value from Damasso *et al.* (unpublished observations).