REFERENCE EDITION | OCTOBER 2026

Antiviral Therapeutics

An encyclopaedic reference across the human virome — molecular mechanism, clinical virology, and bedside decision-making

Every agent is presented at three altitudes: the biochemistry of the drugged step, the laboratory assay that measures it, and the prescription written at the bedside. Recommendations carry IDSA/USPHS two-part evidence grades.

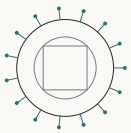
Saranga Sumathipala

Prepared with the assistance of an AI tool (Claude, Anthropic) for drafting and figures. The author directed the work and is responsible for it.



Naked icosahedral

Picorna-, Adeno-, Polyomaviridae



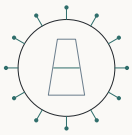
Enveloped icosahedral

Herpes-, Flavi-, Togaviridae



Helical enveloped

Orthomyxo-, Paramyxoviridae



Conical capsid

Retroviridae (HIV-1/2)



Complex brick

Poxviridae (VARV, MPXV)



Filamentous

Filoviridae (EBOV, MARV)

Morphology constrains the druggable step: an envelope invites fusion inhibitors and neutralising antibodies; an ordered capsid invites assembly modulators; a virus-encoded polymerase invites nucleos(t)ide analogues.

Prepared as an educational and decision-support reference for medical practitioners with an interest in infectious diseases. Doses, thresholds, break-points and licensed indications must be verified against current national product labelling, regional guidelines and local antimicrobial stewardship policy before prescribing. Antiviral susceptibility interpretation is assay- and reference-strain-dependent; no CLSI/EUCAST-equivalent universal breakpoint framework exists.

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Use of AI. Prepared with the assistance of an AI tool (Claude, Anthropic), used to draft text and produce the figures. The author directed the work and is responsible for it.

INTENDED AUDIENCE AND READING MODEL

Written for medical practitioners with an interest in infectious diseases — ID and microbiology trainees and consultants, transplant and HIV physicians, intensivists, clinical and molecular virologists, and antimicrobial stewardship pharmacists. It assumes fluency in clinical medicine and does not explain basic pharmacology or immunology.

Every virus chapter is written at **three altitudes**, marked in the margin of the text:

Altitude	What it answers
Molecular virology	Genome class and replication strategy; the precise enzymatic or structural step that is inhibited; the biochemistry of inhibition; why the drug is selective for virus over host; the structural basis of escape.
Clinical virology	Which assay, on which specimen, reported in which units; how to read a viral load trajectory; when and how to order genotypic or phenotypic resistance testing; minority-variant thresholds; therapeutic drug monitoring; the specific pre-analytical traps.
Bedside	Indication, agent, dose, route, duration, renal and hepatic adjustment, interactions, toxicity monitoring, what to do when first-line fails — each with an evidence grade.

EVIDENCE GRADING

Grades follow the **IDSA/USPHS two-part convention** used by the DHHS, IDSA, AST and most antiviral guidance: a letter for the strength of the recommendation and a Roman numeral for the quality of the evidence behind it. A chip such as A-I appears inline.

	Strength of recommendation		Quality of evidence
A	Strong evidence of efficacy with substantial clinical benefit — should always be offered	I	≥1 properly designed randomised controlled trial with clinical endpoints
B	Moderate evidence, or strong evidence of only limited benefit — generally should be offered	II	≥1 well-designed non-randomised trial, observational cohort or case–control study, or an RCT reporting only virological (surrogate) endpoints
C	Evidence insufficient to support for or against, or benefit offset by toxicity, cost or drug interactions — optional	III	Expert opinion, case series, descriptive studies, or *in vitro*/animal data only
D	Moderate evidence against efficacy, or for an adverse outcome — generally should not be offered		
E	Strong evidence against — should never be offered		

A calibration warning that matters more than any single table in this book. Outside HIV, HCV, HBV, influenza and now SARS-CoV-2, the great majority of antiviral practice rests at B-II or C-III. Ganciclovir for HHV-6 encephalitis, cidofovir for adenovirus, ribavirin for respiratory syncytial virus in the immunocompromised, every regimen for BK nephropathy and most of what is written about parainfluenza are *not* supported by randomised clinical-endpoint data. Treating a C-III recommendation as though it were A-I is the commonest intellectual error in inpatient antiviral prescribing, and it is compounded by the fact that many of these agents are substantially toxic. Where no agent has credible evidence, this reference says so explicitly rather than listing something for the sake of completeness.

Caution chips flag a specific hazard — a low resistance barrier, a dose-limiting toxicity, a teratogenic risk, or a treatment that is widely used but poorly supported.

CONVENTIONS

Gene and locus names are italicised (*UL97*); amino-acid substitutions are set as `M460V`, with the herpesvirus/HBV reverse-transcriptase convention of a lower-case prefix where it is standard (`rtM204V`). Viral loads are given in IU/mL where an international standard exists and in copies/mL where it does not — the distinction is not cosmetic and is discussed in §4. Creatinine clearance (CrCl) is by Cockcroft–Gault unless stated, because that is the metric against which antiviral renal dose adjustments were actually derived; eGFR by CKD-EPI is *not* interchangeable at the extremes of body size.

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PART I

Foundations

1 The druggable virus: why antivirals are few, narrow and hard

Antibacterial chemotherapy exploits a separate organism with its own metabolism. Antiviral chemotherapy has no such luxury: a virus is a set of instructions borrowing a human cell's machinery, and almost everything it does, the cell also does. The entire discipline rests on finding the handful of steps that are virus-encoded, essential, structurally distinct from any human counterpart, and accessible to a drug-like molecule.

1.1 The four conditions a target must satisfy

1. **Virus-encoded or virus-conformed.** Either the protein has no human homologue (HIV integrase, CMV terminase pUL56, influenza neuraminidase, HSV helicase–primase) or the human homologue differs enough in active-site architecture to permit discrimination (viral DNA polymerases versus human pol $\alpha/\delta/\gamma$; HIV protease cleaves Phe–Pro bonds that no human endopeptidase cleaves).
2. **Essential and non-redundant.** Loss of function must abolish replication. Accessory proteins (HIV Vpr, Nef) are poor targets because escape is cheap.
3. **Conformationally constrained.** The target must tolerate little sequence variation without losing fitness. This single property *is* the resistance barrier: sofosbuvir is durable because NS5B `S282T` cripples the polymerase, and NNRTIs are fragile because the hydrophobic pocket is dispensable ballast that tolerates `K103N` at negligible cost.
4. **Kinetically accessible.** The drug must reach the compartment where the step occurs — intracellular, often intranuclear, sometimes within the CNS, the eye, genital mucosa or the latent reservoir — at a free concentration above its EC_{50} for a useful fraction of the dosing interval.

1.2 Why the antiviral formulary is small

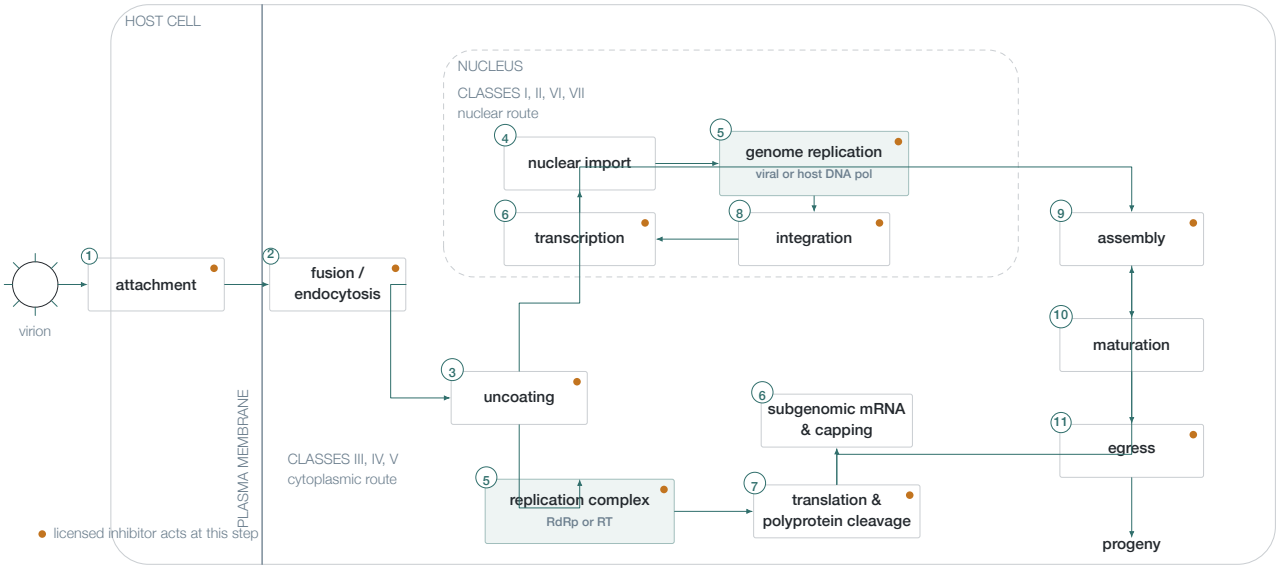
- **Tiny proteomes.** Hepatitis B encodes four genes; SARS-CoV-2 roughly 29 proteins; *Escherichia coli* over 4 000. There is simply less to hit.
- **Host dependency.** Most steps are performed by host enzymes, which cannot be inhibited without toxicity. Classes II (parvovirus) and much of class VII rely on host polymerases, which is precisely why parvovirus B19 has no antiviral.
- **The kinetics of acute infection.** For a self-limited illness that peaks before or at symptom onset — rhinovirus, most enteroviruses, norovirus — a drug started when the patient presents arrives after peak replication. This is a pharmacodynamic impossibility, not a failure of medicinal chemistry, and it explains the graveyard of rhinovirus programmes. It also explains why antiviral efficacy for influenza and SARS-CoV-2 collapses with every day of delay.
- **Narrow spectrum by construction.** Because selectivity derives from virus-specific structure, it is intrinsically non-transferable. Aciclovir is inert against CMV; letermovir is inert against everything except CMV. A "broad-spectrum antiviral" is almost a contradiction in terms, and the few genuinely broad agents — cidofovir, ribavirin, interferon — are broad because their mechanisms are promiscuous, which is the same reason they are toxic.
- **Commercial asymmetry.** Chronic viral infections (HIV, HBV, HCV) attracted sustained investment; acute, sporadic, or geographically confined infections did not. The antiviral pharmacopoeia is a map of market structure as much as of virology.

1.3 Baltimore classification as a target map

The Baltimore scheme — which classifies viruses by genome chemistry and the route taken to mRNA — remains the most useful organising principle for a pharmacologist, because the route to mRNA determines which enzymes must be virus-encoded, and therefore what can be drugged.

Class	Genome	Human families	Virus-encoded replication enzymes	Drugged steps in current practice
I	dsDNA	Herpesviridae, Adenoviridae, Poxviridae, Polyomaviridae, Papillomaviridae	Herpes/pox: own DNA pol, helicase–primase, terminase, thymidine/protein kinases. Adeno: own pol. Polyoma/papilloma: *host* pol (large T as helicase)	DNA polymerase (aciclovir, ganciclovir, foscarnet, cidofovir); terminase (letermovir); helicase–primase (pritelivir, amenamevir); egress p37 (tecovirimat); polyoma/papilloma essentially undruggable
II	ssDNA	Parvoviridae (B19, bocavirus)	None — host pol	*No licensed antiviral.* IVIG for B19 in PRCA B-II
III	dsRNA	Reoviridae (rotavirus)	Own RdRp within the capsid	None licensed; nitazoxanide C-II
IV	(+)ssRNA	Flaviviridae (HCV, DENV, ZIKV, YFV, JEV, WNV, TBEV), Picornaviridae, Coronaviridae, Togaviridae, Hepeviridae, Caliciviridae, Matonaviridae	RdRp, one or more proteases, helicase, methyltransferase, NS5A-type phosphoprotein	RdRp (sofosbuvir, remdesivir, molnupiravir); protease (NS3/4A inhibitors, nirmatrelvir, ensitrelvir); NS5A (velpatasvir class); capsid (pocket binders)
V	(–)ssRNA	Orthomyxoviridae, Paramyxoviridae, Pneumoviridae, Rhabdoviridae, Filoviridae, Arenaviridae, Peribunyaviridae/Nairo-/Hanta-/Phenuiviridae, Henipavirus	RdRp complex (L+P+N), cap-snatching endonuclease, neuraminidase, matrix ion channel	Polymerase (baloxavir on PA endonuclease; remdesivir on L); neuraminidase (oseltamivir class); M2 (amantadine — obsolete); F-protein fusion (nirsevimab, ribavirin by other means)
VI	ssRNA-RT	Retroviridae (HIV-1/2, HTLV-1/2)	Reverse transcriptase, integrase, protease	All five licensed HIV classes plus capsid (lenacapavir) and CCR5 (maraviroc)
VII	dsDNA-RT	Hepadnaviridae (HBV) + its satellite HDV	Reverse transcriptase/pol with RNase H, core protein	RT (tenofovir, entecavir); entry/NTCP (bulevirtide, for HDV); capsid assembly and HBsAg release (investigational)

The replication cycle as an intervention map FIGURE 1.1



1 Attachment	mAbs, maraviroc, bulevirtide	7 Polyprotein cleavage	HIV PIs, NS3/4A PIs, nirmatrelvir, ensitrelvir
2 Fusion / entry	enfuvirtide, prefusion-F mAbs	8 Integration	dolutegravir, bictegravir, cabotegravir
3 Uncoating	amantadine obsolete	9 Assembly	letermovir, lenacapavir, NS5A inhibitors, CpAMs
4 Nuclear import	— no licensed agent	10 Maturation	— investigational only
5 Genome replication	aciclovir, ganciclovir, foscarnet, cidofovir, tenofovir, entecavir, sofosbuvir, remdesivir, NNRTIs	11 Egress / release	oseltamivir, zanamivir, peramivir, tecovirimat
6 Transcription / capping	baloxavir		

FIGURE 1.1. The generic replication cycle resolved into eleven intervention points, separated by replication compartment. Teal boxes mark genome replication, the step carrying the majority of licensed agents; amber bars mark every step for which a licensed inhibitor exists. Steps 5 and 6 appear in both lanes because Baltimore class determines the compartment, not the step. Steps 4 and 10 remain essentially undrugged in human medicine.

1.4 The eleven intervention points

1 — Attachment. Receptor engagement. Drugged by neutralising monoclonal antibodies (the only truly sequence-specific antivirals, and therefore the most fragile to antigenic drift), by receptor antagonists (**maraviroc** at CCR5), and by receptor decoys (**bulevirtide**, a myristoylated preS1 lipopeptide that occupies NTCP).

2 — Fusion or endocytic penetration. **Enfuvirtide** binds the HIV gp41 HR1 groove and prevents six-helix-bundle formation; RSV prefusion-F antibodies (**nirsevimab**, **palivizumab**) lock F in its prefusion state.

3 — Uncoating. The influenza A M2 proton channel (**amantadine**, **rimantadine**) is the historic example and is now of archival interest only: the `S31N` substitution is fixed in essentially all circulating seasonal A strains E (should never be offered).

4 — Nuclear import / genome delivery. Not drugged in licensed practice, although lenacapavir's multi-stage activity includes impaired nuclear import.

5 — Genome replication. The dominant target class: DNA polymerases, RdRps and reverse transcriptases. Chemistry is covered in §2.

6 — Transcription and cap formation. **Baloxavir marboxil** inhibits the cap-dependent endonuclease activity of influenza PA, abolishing cap-snatching.

7 — Polyprotein processing. HIV protease, HCV NS3/4A, SARS-CoV-2 3CL protease (M^{pro}). Blocking maturation yields non-infectious particles.

8 — Integration. INSTIs chelate the two catalytic Mg^{2+} ions of the integrase DDE motif and displace the reactive 3′-adenosine, blocking strand transfer.

9 — Assembly and encapsidation. **Letermovir** blocks the CMV terminase complex (pUL56/pUL89/pUL51) so that concatemeric DNA is neither cleaved nor packaged. **Lenacapavir** binds the HIV capsid hexamer interface. HBV core protein allosteric modulators misdirect capsid assembly.

10 — Maturation. Only investigational agents (HIV maturation inhibitors).

11 — Egress and release. Influenza neuraminidase inhibitors prevent sialic-acid-mediated tethering of nascent virions; **tecovirimat** inhibits the orthopoxvirus p37 (VP37) protein required for wrapping and extracellular virion formation.

1.5 Master index of licensed antiviral mechanisms

Mechanistic class	Molecular target	Representative licensed agents
Obligate chain-terminating nucleoside analogue	Viral DNA pol / RT	aciclovir, valaciclovir, penciclovir, famciclovir, zidovudine, lamivudine, emtricitabine, abacavir
Delayed / non-obligate chain terminator	Viral DNA pol, RdRp	ganciclovir, valganciclovir, remdesivir, obeldesivir, sofosbuvir
Lethal mutagen (error catastrophe)	RdRp fidelity	molnupiravir, favipiravir, ribavirin (partly)
Acyclic nucleoside phosphonate	DNA pol / RT	cidofovir, brincidofovir, adefovir, tenofovir disoproxil, tenofovir alafenamide
Pyrophosphate analogue	PP_i-binding site of DNA pol	foscarnet
Non-nucleoside allosteric polymerase inhibitor	RT pocket, NS5B palm/thumb	efavirenz, rilpivirine, doravirine, etravirine, nevirapine, dasabuvir
Protease inhibitor	HIV PR, NS3/4A, M^{pro}	darunavir, atazanavir, lopinavir, glecaprevir, voxilaprevir, grazoprevir, nirmatrelvir, ensitrelvir
Integrase strand-transfer inhibitor	HIV integrase DDE	dolutegravir, bictegravir, cabotegravir, raltegravir, elvitegravir
Capsid inhibitor	HIV CA hexamer	lenacapavir
NS5A inhibitor	HCV NS5A domain I	velpatasvir, pibrentasvir, ledipasvir, elbasvir, daclatasvir
Terminase inhibitor	CMV pUL56	letermovir
Helicase–primase inhibitor	HSV UL5/UL52	pritelivir, amenamevir
Neuraminidase inhibitor	Influenza NA	oseltamivir, zanamivir, peramivir, laninamivir
Cap-dependent endonuclease inhibitor	Influenza PA	baloxavir marboxil
M2 ion-channel blocker	Influenza A M2	amantadine, rimantadine obsolete
Entry / receptor antagonist	CCR5, NTCP, gp41	maraviroc, bulevirtide, enfuvirtide
Orthopoxvirus egress inhibitor	p37 (VP37)	tecovirimat
Poxvirus DNA pol inhibitor	E9L	brincidofovir, cidofovir
Monoclonal antibody	Surface glycoprotein	nirsevimab, palivizumab, ansuvimab, atoltivimab/maftivimab/odesivimab, ibalizumab (CD4-directed)
Interferons	JAK/STAT induction of ISGs	peginterferon alfa-2a, interferon alfa-2b, peginterferon lambda (limited)
Host nucleotide-pool / pleiotropic	IMPDH, PFOR, sialidase	ribavirin, nitazoxanide, DAS181 (investigational)

2 Molecular pharmacology: activation, inhibition, exposure

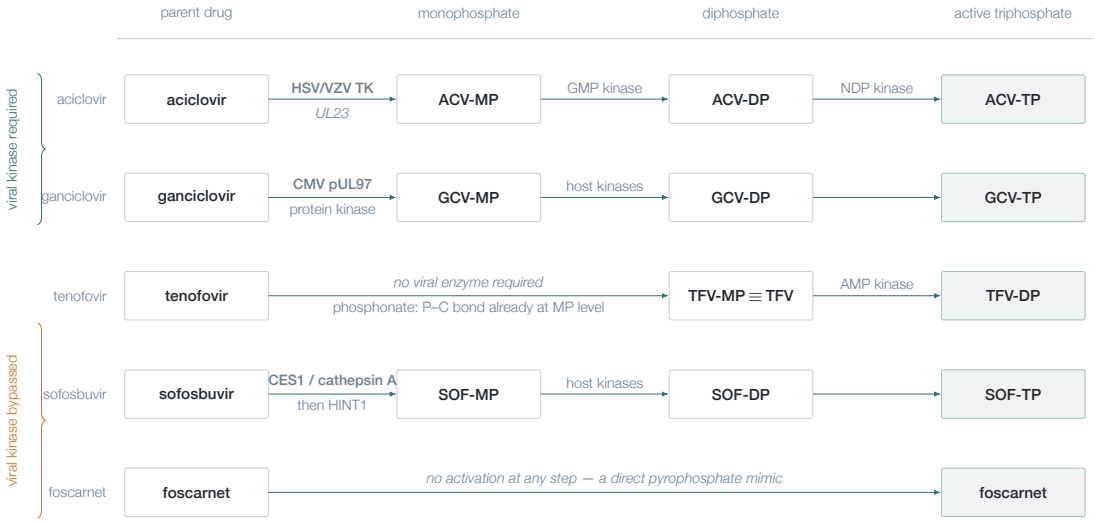
Most antivirals are not drugs when swallowed. They are prodrugs of prodrugs: an ester that survives the gut, a nucleoside that must be phosphorylated three times, a phosphoramidate that must be unmasked by an intracellular esterase. Understanding where each conversion happens explains the drug's selectivity, its tissue distribution, its resistance profile and most of its toxicity.

2.1 The activation problem

A nucleoside analogue is pharmacologically inert. Only the 5′-triphosphate competes with the natural deoxynucleoside triphosphate at the polymerase active site. Three sequential phosphorylations are required, and the **first is almost always rate-limiting and almost always the source of selectivity**.

- **Aciclovir** is monophosphorylated by **HSV/VZV thymidine kinase** (*UL23*), an enzyme with far broader substrate tolerance than human TK1. Uninfected cells therefore accumulate essentially no aciclovir monophosphate. The resulting selectivity index is enormous, which is why aciclovir is one of the safest drugs in medicine — and why **TK-deficient mutants are completely resistant**, the single most important fact about aciclovir failure.
- **Ganciclovir** in CMV is monophosphorylated by the *UL97* phosphotransferase, a protein kinase, not a thymidine kinase (CMV encodes no TK). Hence *UL97* mutations cause ganciclovir resistance without affecting foscarnet or cidofovir.
- **Cidofovir** and **tenofovir** are **phosphonates**: the phosphorus is joined to carbon by a non-hydrolysable P–C bond, so the molecule arrives already at the monophosphate oxidation state. Only two host kinase steps are needed, no viral enzyme is involved, and the spectrum is correspondingly broad — but so is the toxicity, because selectivity now rests entirely on polymerase discrimination.
- **Foscarnet** requires no activation at all. It is a pyrophosphate mimic that occupies the PP_i-release site of the polymerase. This is why it works against TK-deficient HSV and *UL97*-mutant CMV, and why its toxicity (renal tubular injury, profound divalent cation disturbance) is on-target chemistry rather than idiosyncrasy.

Activation routes and the locus of selectivity FIGURE 2.1



Viral kinase required	Selectivity is near-absolute because uninfected cells barely phosphorylate the drug — but a loss-of-function mutation in that kinase (*UL23* in HSV/VZV, *UL97* in CMV) confers complete resistance while leaving the polymerase untouched.
Viral kinase bypassed	Phosphonates arrive at the monophosphate level, ProTides are unmasked by host esterases, and foscarnet needs nothing. Spectrum broadens and kinase-mutant virus remains susceptible — but selectivity now depends solely on the polymerase discriminating drug from natural substrate, which is why these agents are the nephrotoxic, myelotoxic and electrolyte-disturbing end of the formulary.

FIGURE 2.1. Five activation strategies. Agents requiring a virus-encoded kinase (aciclovir, ganciclovir) achieve exceptional selectivity but are disarmed by loss-of-function mutations in that kinase. Phosphonates, ProTides and foscarnet bypass the viral kinase and so retain activity against kinase-mutant virus — the pharmacological basis of every salvage algorithm in herpesvirus medicine.

2.2 Modes of polymerase inhibition

Mode	Structural basis	Consequences for resistance and toxicity
Obligate chain termination	No 3′-OH at all (acyclic sugar, 3′-azido, 3′-deoxy, oxathiolane ring)	Elongation is absolutely blocked. Resistance arises by *discrimination* (the polymerase stops incorporating it) or by *excision* (ATP/PP_i-mediated removal of the terminator — the mechanism of HIV thymidine-analogue mutations). Mitochondrial pol γ off-target activity produces the classic NRTI toxicities.
Delayed (non-obligate) chain termination	3′-OH present; elongation stalls a defined number of nucleotides later through steric clash with the template or the fingers domain	Remdesivir-TP halts coronavirus nsp12 at position $i+3$; because the terminator is buried, it resists excision but is partly removed by the nsp14 exonuclease. Ganciclovir-TP permits short extension before arrest.
Lethal mutagenesis	Ambiguous base-pairing tautomers incorporated as either purine or pyrimidine	Mutation frequency rises above the error threshold and infectivity collapses. Resistance is theoretically very hard, but the mechanism is intrinsically mutagenic — a genuine stewardship and pharmacovigilance consideration for molnupiravir mutagenic mechanism.
Allosteric (non-nucleoside)	Binding to a hydrophobic pocket distant from the catalytic centre, restricting the conformational motion required for catalysis	No activation step, so no kinase-based selectivity; the pocket is dispensable, so single substitutions (K103N, Y181C, E138K) abolish binding at trivial fitness cost low genetic barrier.
Pyrophosphate mimicry	Occupies the PP_i product site, preventing translocation after each incorporation	Active regardless of viral kinase status; resistance requires polymerase mutations that often confer reciprocal hypersusceptibility to other agents.

2.3 Oral prodrug esters and the transporter that makes them work

Aciclovir's oral bioavailability is 10–20%. **Valaciclovir**, its L-valyl ester, is a substrate for the intestinal peptide transporter **PEPT1 (SLC15A1)**, which evolved to absorb di- and tripeptides; first-pass hydrolysis by valacyclovir hydrolase then liberates aciclovir, raising bioavailability to 54%. The identical trick converts ganciclovir (6–9%) to **valganciclovir** (60% *with food*). Three clinical consequences follow:

- Valganciclovir **must** be given with food; fasting administration can lose roughly a third of the exposure and is a recognised cause of apparent CMV treatment failure.
- The tablet and oral-solution formulations of valganciclovir are not bioequivalent milligram for milligram; substituting one for the other without recalculating is a real prescribing error.
- Intravenous ganciclovir 5 mg/kg q12h and oral valganciclovir 900 mg q12h give broadly comparable systemic exposure A-I, which is the pharmacological justification for oral therapy of non-severe CMV disease — but *not* for CNS or retinal disease, where the evidence base is intravenous B-II.

2.4 Exposure parameters that actually drive effect

Agent / class	Plasma t½	Intracellular t½ (active form)	Practical consequence
Tenofovir (as TFV-DP)	12–18 h	~150 h in PBMC/erythrocytes	Forgiving of missed doses; underpins event-driven PrEP dosing and the long washout that confounds adherence assessment
Emtricitabine (FTC-TP)	~10 h	~39 h	Once daily
Abacavir (carbovir-TP)	1.5 h	~20 h	Once daily despite very short plasma half-life
Lamivudine (3TC-TP)	5–7 h	16–19 h	Once daily
Aciclovir	2.5–3 h	~1 h (ACV-TP)	Requires 5× daily dosing for HSV; valaciclovir reduces frequency by raising exposure, not by extending half-life
Ganciclovir	3.5 h (normal renal function)	16–24 h	Twice-daily induction feasible; half-life rises steeply with renal impairment, driving myelotoxicity
Letermovir	12 h	n/a (not a prodrug)	Once daily
Baloxavir	79 h	n/a	**Single dose** treats influenza
Cabotegravir (LA)	5.6–11.5 weeks (IM)	n/a	2-monthly injection; a **pharmacokinetic tail** of months after discontinuation creates a window of subtherapeutic monotherapy and integrase-resistance selection tail risk
Lenacapavir	~8–12 weeks (SC)	n/a	6-monthly dosing; same tail consideration

Inhibitory quotient

The **IQ** is the trough concentration divided by the protein-binding-adjusted EC_{50} for the patient's own virus. The **genotypic IQ** substitutes the number of resistance substitutions for a phenotype. Both were developed for HIV protease inhibitors and remain the most rigorous way to express "is this exposure enough for *this* virus?" They are underused outside HIV, and are the correct conceptual frame when deciding whether to escalate ganciclovir for a *UL97* mutant with a modest fold-change rather than switching to foscarnet.

2.5 Sanctuary compartments

Antiviral failure is frequently a distribution problem rather than a resistance problem.

Compartment	What penetrates, and what this changes
CSF / brain	Aciclovir CSF:plasma ≈0.5 (adequate at 10 mg/kg q8h, the basis of HSV encephalitis dosing); ganciclovir ≈0.3–0.7; foscarnet ≈0.3–0.7; dolutegravir and darunavir adequate; **cidofovir essentially nil**. Tenofovir CNS penetration is poor — relevant to HIV CSF escape. Letermovir CNS penetration is low and it should not be relied upon for CMV CNS disease D-III.
Vitreous / retina	Systemic ganciclovir and foscarnet reach therapeutic vitreous levels slowly; sight-threatening CMV retinitis near the fovea warrants intravitreal ganciclovir or foscarnet *in addition to* systemic therapy A-II, because intravitreal therapy alone does not treat the contralateral eye or viscera.
Genital mucosa	Tenofovir gel/oral concentrations differ markedly between rectal and cervicovaginal tissue — the pharmacological explanation for the divergent efficacy of oral TDF PrEP by exposure route and adherence.
Latent reservoir	No antiviral acts on a transcriptionally silent genome. HSV latency in sensory ganglia, HIV proviral DNA in resting memory $CD4^+$ cells, and HBV cccDNA in hepatocyte nuclei are all *pharmacologically invisible*. This is why suppression is not cure, why HBV relapses on nucleoside withdrawal, and why "antiviral resistance" in HBV must be distinguished from reactivation from a persistent template.

3 Antiviral resistance: evolutionary and molecular principles

Resistance is not an accident of prescribing. It is the predictable output of a population genetic process whose three inputs are mutation supply, selection pressure, and the fitness cost of escape. If you can estimate those three for a given virus–drug pair, you can predict the resistance behaviour of an agent before the first trial reports.

3.1 Mutation supply

Every replication event is a mutagenesis experiment. The number of distinct single mutants generated per day is approximately $\mu \times L \times N$, where μ is the per-site error rate, L the genome length and N the daily production of genomes.

Virus / polymerase	Error rate (substitutions/site/replication)	Genome (kb)	Consequence
HIV-1 RT (no proofreading)	$\sim 10^{-5}$–10^{-4}	9.7	With 10^{10} virions produced daily, **every single and most double mutants pre-exist** before therapy starts. Monotherapy fails by arithmetic, not by chance.
HCV NS5B	$\sim 10^{-5}$–10^{-4}	9.6	Enormous mutant spectra; resistance-associated substitutions are detectable pre-treatment in treatment-naive patients, especially NS5A Y93H in genotype 1a/3.
Influenza RdRp	$\sim 10^{-5}$	13.6 (segmented)	Mutation plus **reassortment**; antigenic and resistance evolution can be saltatory.
Coronaviruses (nsp12 + nsp14-ExoN)	$\sim 10^{-6}$	30	Proofreading exonuclease lowers the error rate roughly tenfold — the reason a 30 kb RNA genome is viable at all, and a partial explanation for remdesivir's modest potency and molnupiravir's mechanism being resisted by ExoN.
Herpesviruses (B-family DNA pol with 3′→5′ exonuclease)	$\sim 10^{-8}$	125–235	Low mutation supply. Resistance requires *prolonged replication under drug pressure*, which is why it is a disease of the profoundly immunocompromised and essentially never of the immunocompetent.
HBV (RT, no proofreading, but via an RNA intermediate)	$\sim 10^{-5}$	3.2	High mutant supply against a tiny, overlapping-reading-frame genome — resistance mutations in *P* necessarily alter *S*, which is why lamivudine resistance can generate vaccine-escape and diagnostic-escape HBsAg variants.
Parvovirus B19, polyoma (host pol)	$\sim 10^{-8}$–10^{-9}	5.0	Host-polymerase fidelity; antiviral resistance is not a meaningful clinical entity, mostly because there are no antivirals.

Practical corollary

Ask of any new antiviral: *how many substitutions are needed, and does the virus make that many per day already?* For HIV, the answer for a single substitution is "millions of times over daily"; monotherapy is therefore never acceptable A-I. For CMV in a healthy host, the answer is "essentially never"; for CMV in a lung transplant recipient on months of valganciclovir with ongoing replication, the answer becomes "routinely".

3.2 Quasispecies, mutant spectra and the error threshold

An RNA virus population is not a clone but a **mutant spectrum** centred on a master sequence, held together by mutation–selection balance. Three clinically important properties follow.

- **Minority variants are the raw material of failure.** A variant at 2% is invisible to Sanger sequencing but can dominate within days of drug exposure.
- **The spectrum itself has phenotype.** Complementation and interference between variants mean the population can behave differently from any of its members.
- **There is an upper limit to tolerable error** (the error threshold, or Eigen limit). Pushing a virus above it collapses infectivity — the explicit design principle of molnupiravir and favipiravir, and part of ribavirin's activity.

3.3 The genetic barrier, formally

The genetic barrier to resistance is the product of three quantities:

1. the **number of substitutions** required to reach a resistant phenotype;

2. the **mutational distance** of each (a transition is roughly an order of magnitude more likely than a transversion; a two-nucleotide codon change is far rarer than one);
3. the **fitness cost** of the resistant variant in the absence of drug, and whether cheap **compensatory mutations** exist to restore it.

Agent	Barrier	Primary escape	Why the barrier is what it is
Sofosbuvir	Very high	`S282T` (NS5B)	Single substitution, but it devastates polymerase processivity; the variant is rarely recovered and does not persist. Chemistry, not combination therapy, provides the barrier.
Dolutegravir, bictegravir	Very high	`R263K`, `G118R`	Second-generation INSTI binding tolerates the first-generation pathways; escape mutations carry a steep replication-capacity cost with few good compensators.
Boosted darunavir	Very high	multiple PI mutations	Requires accumulation of many substitutions; virological failure on darunavir/r monotherapy usually reveals *no* resistance, only non-adherence.
Letermovir	**Low**	`UL56 C325Y/W/F`	A single substitution confers >3000-fold resistance at modest fitness cost low barrier. This is the central reason letermovir is a prophylactic agent and not a treatment agent D-II for established disease.
Lamivudine (HBV)	Low	`rtM204V/I` ± `rtL180M`	Single primary substitution; ~70% resistance by five years of monotherapy obsolete as monotherapy.
Entecavir (in a nucleoside-naive patient)	High	requires `rtM204V` *plus* `rtT184`/`rtS202`/`rtM250`	Three substitutions needed; ~1.2% at five years. **But** in a lamivudine-experienced patient the first substitution is already present and the barrier collapses to ~50% at five years — the single most important fact in HBV prescribing never use entecavir after lamivudine failure.
Tenofovir (HBV)	Very high	no clinically established pathway	No confirmed tenofovir resistance after a decade of monotherapy; the agent of choice in any nucleoside-experienced patient A-I.
NNRTIs (1st generation)	Low	`K103N`, `Y181C`	Single substitution, negligible fitness cost, and `K103N` persists for years as an archived variant low barrier.
Oseltamivir	Moderate	`H275Y` (N1), `R292K` (N2)	`H275Y` once carried a fitness cost, but permissive secondary substitutions (`R222Q`, `V234M`) restored fitness in the 2007–09 seasonal H1N1 lineage and the resistant variant spread globally *in the absence of drug pressure* — the definitive demonstration that compensatory evolution can abolish a barrier.
Baloxavir	**Low**	`PA I38T/M/F`	Emerges in 2–10% of treated adults and up to 20–25% of treated children within days treatment-emergent in children.
Nirmatrelvir	Moderate–high	`E166V`, `L50F+E166V`	Escape substitutions impair M^{pro} function; clinically significant resistance has remained uncommon, though it is documented in prolonged immunocompromised infection.

3.4 Mechanistic classes of resistance

Loss of activating enzyme. The commonest mechanism in herpesviruses: ~95% of aciclovir-resistant HSV carries *UL23* (TK) mutations — frameshifts in homopolymer runs (G-strings at codons 146 and 430), nonsense mutations, or substitutions altering substrate specificity. The virus becomes resistant by becoming *less* enzymatically capable, which is why TK-deficient HSV is also less neurovirulent and less able to reactivate from latency.

Altered target: discrimination. The polymerase simply stops selecting the analogue (`K65R`, `M184V` in HIV RT; `S282T` in NS5B).

Altered target: excision. Thymidine-analogue mutations (`M41L`, `D67N`, `K70R`, `L210W`, `T215Y/F`, `K219Q/E`) enhance ATP-dependent pyrophosphorolytic removal of the incorporated terminator. Note the elegant antagonism: `M184V` and `K65R` *impair* excision, so lamivudine/emtricitabine partially resensitises zidovudine-resistant virus — a reason to retain 3TC/FTC in a failing regimen.

Loss of an allosteric pocket. NNRTI and NS5B non-nucleoside pockets.

Altered drug-binding surface on a structural protein. Influenza M2 `S31N`; neuraminidase `H275Y`; monoclonal antibody epitope drift (the entire history of SARS-CoV-2 mAbs).

Reduced intracellular accumulation. Rarely a dominant mechanism in virology, unlike bacteriology — there is no viral efflux pump. Host transporter polymorphisms (*SLCO1B1*, *ABCB1*) affect exposure, not viral susceptibility.

Pseudoresistance. Failure that is not resistance at all: non-adherence, malabsorption, a drug interaction, inadequate dosing in augmented renal clearance, a sanctuary site, or ongoing replication from a latent template. **In most antiviral failures this is the answer**, and it should be excluded before resistance testing is ordered.

3.5 Transmitted, acquired and archived resistance

- **Transmitted drug resistance** matters where it changes empirical therapy: pretreatment NNRTI resistance exceeds 10% in many settings, which is the principal public health argument for dolutegravir-based first-line ART A-I.
- **Archived resistance** resides in integrated proviral DNA and in HBV cccDNA. A plasma RNA genotype in a virally suppressed patient cannot see it; proviral DNA genotyping can, with the caveat that much of what it detects is defective, non-replication-competent sequence and so over-calls resistance interpret with care.
- **Reversion.** In the absence of drug, costly resistant variants are outgrown by wild type in plasma but persist in the archive. A "clean" genotype after a treatment interruption is therefore not evidence of absent resistance A-II.

4 Antiviral resistance testing: history, methods, principles

Every resistance assay answers one of exactly two questions. *Phenotypic* assays ask: how much drug does it take to inhibit this virus? *Genotypic* assays ask: does this virus carry sequence changes previously shown to raise that number? The first is the ground truth but is slow, expensive and poorly standardised. The second is fast and cheap but is only as good as the database behind it. Almost every controversy in this field is a consequence of substituting the second for the first without saying so.

4.1 The logic of a susceptibility measurement

Phenotypic antiviral susceptibility is expressed as the **IC_{50} or EC_{50}** — the concentration inhibiting 50% of a measured viral function — and, clinically, as the **fold change** relative to a reference strain run in the same assay on the same day. There is no universal breakpoint framework: unlike CLSI or EUCAST in bacteriology, antiviral "resistance" thresholds are defined per-virus, per-assay, per-laboratory, and are usually expressed as a multiple of a wild-type control rather than an absolute concentration. This has four practical implications.

1. **An IC_{50} in isolation is uninterpretable.** It must be accompanied by the contemporaneous reference-strain value and the assay's own resistance cut-off.
2. **Cut-offs are statistical, not pharmacological.** A "biological cut-off" is the upper bound of the wild-type distribution; a "clinical cut-off" is the fold change above which treatment response demonstrably falls. Most antiviral cut-offs are biological. Only HIV has well-established clinical cut-offs, and only for some agents.
3. **Fold change is assay-dependent.** The same CMV isolate may give a 4-fold change by plaque reduction and a 7-fold change by a reporter assay.
4. **Cell line matters.** Susceptibility depends on host nucleotide pools and kinase expression; aciclovir IC_{50} differs between Vero and human fibroblasts.

Six decades of resistance testing: what each method can and cannot see FIGURE 4.1

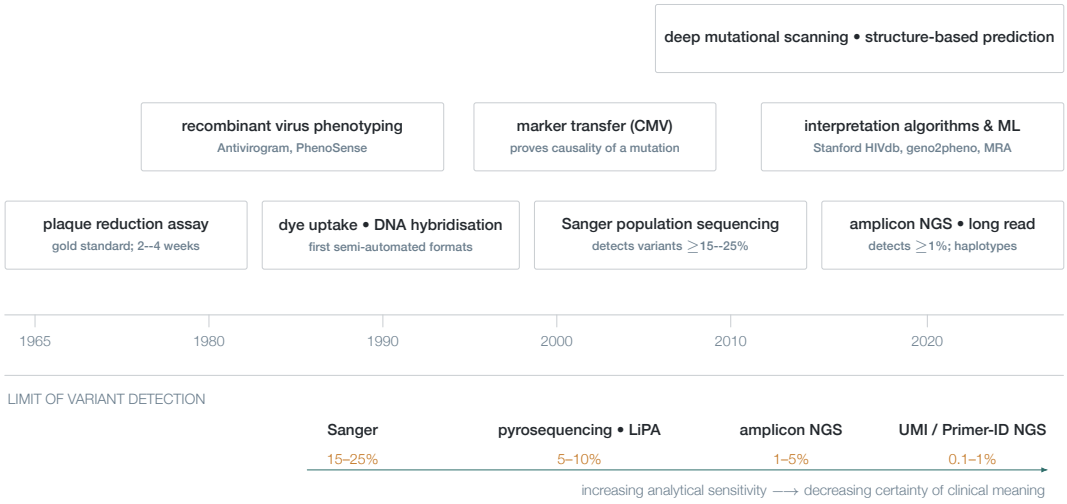


FIGURE 4.1. The field moved from measuring virus growth, to measuring sequence, to measuring sequence at ever-lower abundance. Each step gained speed and lost direct evidence of phenotype. The unresolved question of the NGS era is not whether a 2% variant can be detected — it can — but whether it matters.

4.2 Historical phenotypic methods, and why they still define the field

Plaque reduction assay (PRA)

The reference method since the 1960s and still the formal gold standard for HSV, VZV and CMV. Virus is titrated onto a confluent monolayer (human foreskin fibroblasts for CMV; Vero or HFF for HSV) under semisolid overlay with graded drug concentrations; plaques are counted after incubation and the concentration reducing plaque number by 50% is interpolated. **Scientific basis:** it measures the complete replication cycle including entry, replication, assembly and cell-to-cell spread, so it captures any mechanism of resistance, including ones nobody has characterised. **Limitations:** requires viral isolation in culture (impossible for many specimens and for non-culturable viruses such as BK or HCV), takes 2–4 weeks for CMV, is labour-intensive, reads out subjectively, and has notoriously poor inter-laboratory

reproducibility — interlaboratory coefficients of variation of 30–50% were documented for CMV PRA, which is precisely why genotype displaced it.

Dye uptake, DNA hybridisation and yield reduction

The dye uptake assay (neutral red uptake by surviving cells) and the DNA hybridisation assay (quantifying viral DNA with a labelled probe, commercialised as the Hybriwix format) were the first semi-automated alternatives: faster, more objective, more reproducible, but measuring a surrogate (cell viability or DNA accumulation) rather than infectious progeny. The **yield reduction assay** quantifies infectious virus produced after a single cycle and remains useful where cell-to-cell spread confounds PRA.

Enzyme-based and reporter assays

For influenza, the historic and still-standard phenotypic test is not a growth assay at all but an **enzyme inhibition assay**: the fluorogenic substrate MUNANA (2′-(4-methylumbelliferyl)-α-D-*N*-acetylneuraminic acid) is cleaved by neuraminidase to release a fluorophore, and IC_{50} is determined directly against the enzyme. This is elegant because the target is a surface enzyme accessible in a cell-free format, and because it is quantitative and standardisable — the WHO Antiviral Working Group defines *reduced inhibition* as 10–100-fold (influenza A) or 5–50-fold (influenza B) and *highly reduced inhibition* above those, deliberately avoiding the word “resistant” because the clinical correlate is imperfect. Note the crucial corollary: **the MUNANA assay cannot detect resistance to baloxavir or to M2 blockers**, because they do not act on neuraminidase. Reporter-gene viruses (luciferase, GFP) now provide rapid, objective, high-throughput phenotyping for HIV, HCV and SARS-CoV-2.

Recombinant virus assays

The decisive innovation for HIV. Patient-derived *pol* (or *env*, or *gag-pro*) is amplified from plasma and recombined into a standardised laboratory backbone carrying a reporter gene; susceptibility is read as reporter output across a drug gradient. The two historic commercial platforms were **Antivirogram** (homologous recombination in cells) and **PhenoSense** (ligation into a resistance-test vector). The same assay yields **replication capacity**, a measure of fitness relative to wild type that informs whether to keep a failing agent such as lamivudine in place to maintain a costly `M184V`. **Limitation:** the chimera has patient sequence only in the cloned region, so resistance determinants outside it — Gag cleavage-site mutations affecting protease inhibitor susceptibility are the classic example — are invisible.

Marker transfer: the assay that establishes causality

Genotype-to-phenotype inference requires proof that a given substitution *causes* the resistance, not merely that it travels with it. **Marker transfer** does this: the candidate mutation is engineered into a defined laboratory background (for CMV, by bacterial-artificial-chromosome recombineering of the AD169 or Towne genome; for HIV, by site-directed mutagenesis of NL4-3) and the recombinant’s susceptibility is measured directly. Essentially every entry in a CMV resistance database that is labelled “confirmed” rests on a marker-transfer experiment. When you read a report stating that a novel *UL54* variant is “of unknown significance”, what is meant is that no one has yet performed this experiment.

4.3 Genotypic methods

Sanger population sequencing

Still the workhorse. Target genes are amplified and sequenced bidirectionally; the electropherogram represents the population average, with mixtures appearing as superimposed peaks. **Analytical sensitivity for a minority variant is 15–25%** — a hard, chemistry-imposed floor. **Requirements:** adequate viral load (typically >500–1000 IU/mL for HIV, and for CMV generally >1000 IU/mL in plasma, higher in some assays), and sufficient amplicon coverage of the relevant genes. **Virus-specific targets:**

Virus	Genes sequenced	Notes
HIV-1	*pol* (protease, RT), *integrase* as a separate request; *env* V3 for tropism	Integrase is *not* included by default in most assays — it must be requested. Proviral DNA genotyping is used in suppressed patients.
CMV	*UL97* (codons 440–645), *UL54* (codons 300–1000), *UL56* (codons 230–370)	*UL56*/*UL89*/*UL51* only if letermovir has been used; *UL27* for maribavir alongside *UL97*.
HSV / VZV	*UL23* (TK) and *UL30* (pol); VZV *ORF36* and *ORF28*	Interpretation is uniquely difficult: *UL23* tolerates abundant natural polymorphism, and distinguishing a resistance frameshift from a benign variant often requires phenotype or marker transfer.
HBV	*RT* domain of *P* (codons rt1–rt344)	Reported with the `rt` prefix; remember the overlapping *S* reading frame.
HCV	*NS3*, *NS5A*, *NS5B*	NS5A RASs are the only ones that routinely alter management; baseline testing is largely obsolete with pangenotypic regimens.
Influenza	*NA*, *PA*, *M2*	Sequence-based screening for `H275Y`, `I38T`, `S31N`.
SARS-CoV-2	*nsp5* (M^{pro}), *nsp12*, *S*	Usually from whole-genome surveillance data rather than a dedicated assay.

Targeted and hybridisation-based methods

Line probe assays (reverse hybridisation to immobilised oligonucleotide probes; INNO-LiPA for HBV and historically for HCV) detect a predefined set of substitutions down to roughly 5% abundance, rapidly and without sequencing infrastructure. **Allele-specific real-time PCR** and **digital droplet PCR** achieve 0.1–1% sensitivity for a single known substitution and are the method of choice when you need to quantify one variant precisely (for example, tracking `H275Y` during an outbreak). **Pyrosequencing** occupies a middle position at 5–10%. All share the same fundamental constraint: **they can only find what they were designed to find**, and are therefore blind to novel resistance.

Next-generation sequencing

Amplicon deep sequencing routinely resolves variants to 1–5%, and with molecular barcoding (unique molecular identifiers, Primer-ID) to below 0.1% by distinguishing true variants from PCR and sequencing error. **Long-read platforms** add what short reads cannot provide: **linkage**. Knowing that `rtL180M` and `rtM204V` are on the same genome, rather than in two separate viral populations, changes the interpretation entirely, and short-read amplicon data cannot establish it.

THE UNSOLVED PROBLEM OF THE NGS ERA

Lowering the detection threshold does not automatically improve care. For HIV, minority NNRTI variants above roughly 1% are associated with virological failure of an NNRTI regimen B-II, but minority variants below that threshold generally are not, and reporting them causes regimens to be abandoned without benefit. For CMV, no validated clinical threshold exists at all; most laboratories report at 5–10% and flag lower-level findings as uncertain C-III. **The correct question is never "what is the lowest level we can detect" but "at what level does a variant change the outcome"** — and for most viruses that number has not been determined. Report minority variants with an explicit abundance figure, never as a binary "resistance detected".

4.4 Interpretation systems

A genotype is a list of substitutions; a report is an inference. The inference is produced by a rules-based or statistical algorithm, and different algorithms disagree.

System	Virus	Method and caveats
Stanford HIV Drug Resistance Database (HIVdb)	HIV-1/2	Expert-curated mutation-penalty scoring producing five susceptibility levels. The de facto international standard; updated continuously; freely available.
ANRS, Rega	HIV-1	Independent rules sets; differ from HIVdb in roughly 5–10% of interpretations, usually at the boundary between intermediate and resistant.
geno2pheno	HIV-1 (coreceptor and drug resistance), HCV	A statistical/machine-learning approach rather than a rules set; for tropism it reports a **false-positive rate** (FPR), with a clinical cut-off around 10% — a probabilistic output requiring a probabilistic reading.
Mutation Resistance Analyzer (MRA)	CMV	Curated database of *UL97*, *UL54*, *UL56* and *UL27* substitutions with marker-transfer-confirmed fold changes. The appropriate reference for any CMV genotype report.
HBV and HSV	—	No universally accepted algorithm; interpretation rests on literature review and, for HSV, frequently on phenotype.

4.5 Quality, standardisation and the things that go wrong

- **Reference strains.** CMV AD169 and Towne; HSV-1 KOS or 17syn+; HIV NL4-3 or HXB2 (which also supplies the universal numbering convention). Every fold change is relative to one of these.
- **International standards.** WHO international standards exist for CMV, EBV, BKV, HBV, HCV, HIV and adenovirus, permitting results in **IU/mL**. Where no standard exists, results are in copies/mL and **are not comparable between laboratories or platforms** — a difference that has caused real clinical errors when patients transfer between centres.
- **External quality assessment.** QCMD and equivalent schemes cover molecular virology broadly; coverage of resistance genotyping specifically is thinner.
- **Pre-analytical failures.** Insufficient viral load for amplification is the commonest reason a resistance test fails; sampling the wrong compartment is the commonest reason it misleads. CMV resistance mutations may be present in a compartment (vitreous, CSF, gut biopsy, BAL) and absent from plasma.
- **The timing error.** Resistance testing must be performed **on therapy, or within four weeks of stopping**. Once drug pressure is removed, wild type outgrows the resistant variant in plasma and the test returns a falsely reassuring result A-II.

4.6 When to test: a practical algorithm

1. **Confirm there is true virological failure** — a rising or non-declining viral load on adequate therapy, measured on the same platform, confirmed on a repeat sample.
2. **Exclude pseudoresistance first**: adherence, absorption (food effects, gastrostomy administration, diarrhoea, bariatric anatomy), drug interactions (proton pump inhibitors with rilpivirine or atazanavir; rifampicin with almost everything), underdosing in obesity or augmented renal clearance, and a sanctuary compartment. This step resolves the majority of cases.
3. **Check the biological plausibility**: has there been sufficient duration of replication under drug pressure? Aciclovir-resistant HSV after five days of therapy in an immunocompetent adult is close to impossible; after six weeks in a haematopoietic cell transplant recipient it is likely.
4. **Order the right genes**, on the right specimen, while the patient is still on drug.
5. **Interpret the report with the algorithm and the fold changes**, not from the mutation list alone, and escalate to phenotype or specialist advice when a variant is novel or the genotype does not explain the clinical picture.

5 Clinical virology measurement and decision-making

A viral load is not a number. It is a number produced by a particular assay, on a particular specimen type, from a particular compartment, calibrated (or not) to an international standard, with its own linear range, precision and biological variability. Decisions made without knowing those five things are made on noise.

5.1 IU/mL versus copies/mL

Where a WHO International Standard exists, results should be reported in **international units per millilitre**. The standard is a lyophilised, characterised preparation to which assays are calibrated, so results become comparable between platforms and laboratories. Standards exist for CMV, EBV, BKV, adenovirus, HBV, HCV, HIV-1, HPV and others.

Three traps follow:

- **The conversion factor between IU and copies is assay-specific**, commonly between 0.5 and 5 copies per IU, and is not transferable.
- **Calibration to a standard does not abolish inter-assay variability.** Even IU-calibrated CMV assays can differ by 0.5 $\log_{10}$ because of differences in amplicon target, extraction efficiency and the proportion of fragmented DNA detected.
- **Never compare results across platforms during a treatment course.** If a patient transfers between centres, re-baseline on the new assay before concluding that therapy is failing A-III.

5.2 What counts as a real change

The analytical and biological variability of most quantitative viral assays means a change of less than **0.5 $\log_{10}$ (roughly 3-fold)** is within noise, and for many herpesvirus assays the threshold for significance is nearer **0.5–1.0 $\log_{10}$**. Clinical corollaries:

- A CMV DNAemia rising from 1 200 to 2 600 IU/mL is not necessarily rising.
- An HIV "blip" (a single detectable value, typically <200 copies/mL, with re-suppression) does not indicate failure and does not warrant resistance testing A-II.
- Confirmed, sustained HIV viraemia >200 copies/mL *is* virological failure and does warrant investigation A-I.

5.3 Specimen and compartment

Virus	Preferred specimen	Interpretive notes
CMV	**Plasma** (preferred over whole blood for monitoring)	Whole blood gives values roughly 0.5–1 $\log_{10}$ higher and includes leucocyte-associated DNA; do not switch mid-course. Compartmental disease (retinitis, colitis, pneumonitis, CNS) can occur with **undetectable plasma DNAemia** — a negative plasma PCR does not exclude tissue-invasive CMV A-II.
EBV	Whole blood or plasma	Plasma correlates better with lymphoproliferative disease; whole blood detects latent genomes in B cells and is less specific. Chronic low-level whole-blood positivity is common and usually meaningless.
BK virus	Plasma *and* urine	Urinary BK is present in up to 30% of transplant recipients and is not nephropathy. Plasma DNAemia, particularly sustained $>10^4$ copies/mL, is the actionable signal.
HSV / VZV	Lesion swab, CSF, vitreous	CSF PCR is the diagnostic standard for encephalitis; it may be **negative in the first 72 hours** of HSV encephalitis, and a negative early result in a compatible illness must be repeated rather than used to stop aciclovir A-II.
Respiratory viruses	Nasopharyngeal swab; BAL in the immunocompromised	Upper-tract sampling can miss lower-tract influenza, RSV or adenovirus in immunocompromised and ventilated patients.
Adenovirus	Plasma	Rising plasma DNAemia precedes disseminated disease in HCT recipients and is the trigger for pre-emptive therapy.
Enterovirus/parechovirus	CSF, throat, stool	Stool positivity may persist for weeks and does not prove current CNS disease.

5.4 Therapeutic drug monitoring in antiviral therapy

TDM is underused but genuinely indicated in defined circumstances.

Agent	Target (indicative)	When to measure, and why
Ganciclovir	Trough <2 mg/L; peak 8–12 mg/L	Renal impairment, CRRT, ECMO, obesity, unexplained myelotoxicity, or failure to clear DNAemia despite susceptible virus B-II.
Foscarnet	Not routine	Monitored clinically by renal function and ionised calcium rather than by concentration.
Ribavirin (oral, chronic)	Trough 2–3 mg/L (historical HCV)	Anaemia correlates with exposure; largely of historical interest.
Efavirenz	1–4 mg/L	CNS toxicity above range; *CYP2B6* slow metabolisers (common in African and Southeast Asian populations) reach very high concentrations B-II.
Protease inhibitors	Variable by agent	Pregnancy, malabsorption, drug interactions, paediatric dosing, suspected non-adherence.
Letermovir, maribavir	Not established	No validated targets.
Oseltamivir (critical care)	Not routine	Carboxylate exposure is reduced in ECMO circuits and CRRT; dose adjustment is empirical.

THE THREE QUESTIONS TO ASK BEFORE ACTING ON ANY VIRAL LOAD

1. Is this assay IU-calibrated, and is it the same assay as last time? 2. Is the change larger than 0.5 $\log_{10}$? 3. Does this compartment answer the clinical question I am asking? If the answer to any is no, the correct next step is another measurement, not another drug.

6 Dose adjustment and special populations

Most antivirals in hospital practice are renally cleared, and most antiviral toxicity in hospital practice is a consequence of failing to adjust for that. Conversely, reflexive dose reduction in the setting of augmented renal clearance or extracorporeal therapy is a common and under-recognised cause of treatment failure and of resistance emergence.

6.1 Principles

1. **Use Cockcroft–Gault creatinine clearance, not eGFR**, for antiviral dose adjustment. Every antiviral renal dosing table in existence was derived against CrCl. CKD-EPI eGFR is normalised to 1.73 m^2 and diverges substantially at the extremes of body size — systematically overdosing the small elderly patient and underdosing the large one A-III.
2. **Distinguish loading from maintenance.** Loading doses depend on volume of distribution and should *not* be reduced for renal impairment; only maintenance doses are adjusted. Reducing the first dose of aciclovir in HSV encephalitis delays therapeutic concentrations at the only time they matter.
3. **Beware augmented renal clearance** (CrCl >130 mL/min), common in young patients with sepsis, burns, trauma and neurocritical illness. Standard aciclovir and ganciclovir doses may be subtherapeutic.
4. **Adjust for the active moiety, not the prodrug.** Valganciclovir dose adjustment tables reflect ganciclovir exposure.
5. **Weight.** Aciclovir should be dosed on **ideal body weight** in obesity — dosing a 160 kg patient on actual body weight is a recognised cause of crystal nephropathy and neurotoxicity A-II. Ganciclovir is conventionally dosed on actual body weight but adjusted body weight is reasonable in extreme obesity C-III.

6.2 Renal dose adjustment: core agents

Agent	Normal renal function	Adjustment principle	Notes
Aciclovir IV	5–10 mg/kg q8h (10 mg/kg for encephalitis, VZV in the immunocompromised)	Reduce frequency progressively; at CrCl <10 give approximately half the dose once daily	Dose on ideal body weight. Ensure vigorous hydration and infuse over ≥1 h to prevent crystal nephropathy. Neurotoxicity (tremor, myoclonus, hallucinations, "aciclovir delirium") is dose- and metabolite-related and is frequently misattributed to the encephalitis itself.
Valaciclovir	1 g tds (zoster)	Reduce dose and interval by CrCl	Thrombotic microangiopathy reported at very high doses in advanced HIV/transplant rare, severe.
Ganciclovir IV	Induction 5 mg/kg q12h; maintenance 5 mg/kg daily	Reduce both dose and interval; substantial reductions below CrCl 50	Dose-limiting neutropenia and thrombocytopenia; check FBC at least twice weekly during induction. G-CSF is preferable to dose reduction when the virus is still replicating.
Valganciclovir	900 mg bd induction; 900 mg daily maintenance	Stepwise reduction by CrCl; not recommended on haemodialysis (use IV ganciclovir)	Must be taken with food.
Foscarnet	Induction 60 mg/kg q8h or 90 mg/kg q12h	Weight- and CrCl-indexed nomogram; small changes in CrCl require recalculation	Requires pre- and post-hydration with saline. Causes renal tubular wasting of calcium, magnesium, potassium and phosphate; monitor ionised calcium and replace aggressively. Genital ulceration is a characteristic adverse effect.
Cidofovir	5 mg/kg weekly ×2 then fortnightly	Contraindicated if creatinine >133 μmol/L, CrCl ≤55 mL/min or proteinuria ≥2+	**Mandatory** probenecid (2 g before, 1 g at 2 and 8 hours after) plus 1 L saline pre-hydration, to block OAT1-mediated proximal tubular uptake A-I. Nephrotoxicity is otherwise frequent and can be irreversible.
Remdesivir	200 mg then 100 mg daily	No adjustment required in current labelling across the renal range, including dialysis	The earlier eGFR <30 restriction related to accumulation of the SBECD vehicle and has been superseded by data showing acceptable safety B-II.
Oseltamivir	75 mg bd	30 mg bd at CrCl 30–60; 30 mg daily at CrCl 10–30; dose after dialysis sessions	Dose doubling for severe influenza is not supported by trial data D-I.
Tenofovir disoproxil	245 mg daily	Interval extension below CrCl 50	Prefer tenofovir alafenamide in renal or bone disease; TAF requires no adjustment to CrCl 30 A-I.
Letermovir	480 mg daily (240 mg with ciclosporin)	No renal adjustment	Reduce to 240 mg with ciclosporin because of OATP1B1 inhibition.

6.3 Renal replacement therapy and extracorporeal circuits

- **Intermittent haemodialysis.** Aciclovir, ganciclovir, foscarnet and oseltamivir carboxylate are all substantially dialysed. Give the dose **after** the session.
- **CRRT** provides continuous clearance that is typically equivalent to a CrCl of 25–50 mL/min, so doses reduced to an anuric schedule will be subtherapeutic. For ganciclovir on CVVHDF, approximately 2.5 mg/kg every 24 hours is a common starting point, with TDM B-III.
- **ECMO.** Circuit sequestration is significant for lipophilic, highly protein-bound drugs; most antivirals are hydrophilic and less affected, but the volume of distribution is increased and clearance is often augmented. Under-dosing is the greater risk.
- **Plasma exchange** removes highly protein-bound agents; redose after the procedure where a drug is >80% bound and has a small volume of distribution.

6.4 Hepatic impairment

Few antivirals require hepatic adjustment, but the exceptions are important and several are absolute contraindications.

- **HCV protease inhibitors** (glecaprevir/pibrentasvir, sofosbuvir/velpatasvir/voxilaprevir, grazoprevir/elbasvir) are **contraindicated in Child–Pugh B and C** E-I, because protease-inhibitor exposure rises severalfold and hepatic decompensation has occurred. Sofosbuvir/velpatasvir (no protease inhibitor) is the pangenotypic regimen of choice in decompensated cirrhosis, with ribavirin A-I.
- **Nevirapine** is contraindicated in moderate–severe hepatic impairment.
- **Maraviroc** exposure rises in hepatic impairment.
- **Nucleos(t)ide analogues for HBV are not dose-reduced for hepatic impairment**; they are the treatment for it.

6.5 Pregnancy

Agent	Position	Comment
Aciclovir, valaciclovir	Extensive safety data	No increase in birth defects across large registries; used for HSV suppression from 36 weeks to reduce caesarean for recurrent genital herpes A-I, and for maternal varicella B-II.
Tenofovir disoproxil, lamivudine, emtricitabine	Preferred	Backbone of ART in pregnancy; TDF also used for HBV prevention of mother-to-child transmission from 28 weeks when maternal DNA >200 000 IU/mL A-I.
Dolutegravir	Recommended	The early neural-tube-defect signal from Botswana was not confirmed with accumulating data; dolutegravir is now recommended throughout pregnancy and at conception A-II.
Ribavirin	**Contraindicated**	Potently teratogenic and embryolethal. Effective contraception required during therapy and for **6 months** afterwards, in women and in female partners of treated men E-II.
Ganciclovir, valganciclovir	Avoid	Teratogenic and carcinogenic in animals; use only when benefit clearly outweighs risk.
Cidofovir	Avoid	Embryotoxic and carcinogenic in animals.
Molnupiravir	**Avoid**	Mutagenic mechanism; contraindicated in pregnancy E-III.
Nirmatrelvir/ritonavir	Acceptable	Limited but reassuring data; the interaction burden is the practical constraint.
Oseltamivir	Recommended	Pregnant and recently postpartum women are a priority group for early treatment of influenza A-II.
Interferon alfa	Avoid	Abortifacient in animals.

6.6 Children

Paediatric antiviral dosing is not simply weight-scaled adult dosing. Clearance per kilogram is higher in infants and young children for most renally cleared antivirals, and several agents have distinct paediatric regimens.

- **Aciclovir** for neonatal HSV requires 20 mg/kg q8h for 14 days (skin–eye–mouth) or 21 days (disseminated or CNS disease) A-I, followed by 6 months of oral suppressive valaciclovir, which improves neurodevelopmental outcome A-I.
- **Valganciclovir** for symptomatic congenital CMV: 16 mg/kg twice daily for 6 months improves hearing and neurodevelopmental outcomes A-I. Six months is superior to six weeks.
- **Oseltamivir** dosing is banded by weight; infants under one year require 3 mg/kg twice daily.
- **Baloxavir** carries a notably higher rate of treatment-emergent `PA I38X` resistance in children (up to 20–25%) paediatric resistance.

7 Antiviral stewardship

Antimicrobial stewardship grew up around antibacterials, and most programmes still treat antivirals as an afterthought. This is a mistake on every axis that matters: antivirals are among the most expensive agents on the formulary, several are profoundly toxic, their interaction burden is the highest in the hospital, resistance is both selectable and transmissible, and the commonest error — continuing a drug that was never indicated — is invisible to the metrics antibacterial stewardship uses.

7.1 Why antivirals need their own stewardship logic

- **The diagnostic trigger is usually a PCR result, not a culture.** A positive PCR may represent disease, asymptomatic shedding, latent genome detection, or contamination. CMV DNAemia, urinary BK, whole-blood EBV, stool enterovirus and respiratory rhinovirus are all routinely over-treated for exactly this reason.
- **The evidence base is weaker than prescribers assume.** The calibration warning in the front matter is a stewardship instrument: a large fraction of inpatient antiviral use rests on C-III recommendations.
- **Toxicity is frequently dose-related and preventable.** Aciclovir crystal nephropathy and neurotoxicity, ganciclovir cytopenias, foscarnet electrolyte catastrophe and cidofovir nephrotoxicity are all largely functions of dosing and monitoring practice.
- **Cost is concentrated.** Letermovir, maribavir, remdesivir, nirsevimab, long-acting cabotegravir and the DAAs dominate pharmacy expenditure out of proportion to the number of courses.
- **Interactions are the dominant safety signal.** Ritonavir- and cobicistat-boosted regimens, letermovir with calcineurin inhibitors, and rifamycins with almost every antiviral generate more preventable harm than antiviral toxicity itself.

7.2 The five stewardship questions

1. **Is there disease, or only detection?** Distinguish replication from disease, and disease from colonisation or latency. Demand a syndrome, not a result.
2. **Is the agent active, at an adequate dose, in the right compartment?** Most "resistance" is pseudoresistance (§3.4).
3. **What is the stop date?** Antiviral courses drift. Define duration and the clinical or virological endpoint at the moment of prescribing.
4. **Can it be de-escalated or oralised?** IV ganciclovir to oral valganciclovir, IV aciclovir to oral valaciclovir, and IV to oral switch for stable patients is the single largest avoidable cost and line-infection burden in antiviral practice.
5. **What is being monitored, by whom, and how often?** Every antiviral with dose-limiting toxicity needs a named monitoring plan.

7.3 High-yield stewardship interventions

Intervention	Rationale and expected effect
Restrict and pre-authorise high-cost or high-toxicity agents (cidofovir, foscarnet, maribavir, letermovir, remdesivir, nirsevimab)	Forces a documented indication and a specialist conversation at the point of greatest leverage, before the first dose B-II.
Automatic stop dates for empirical aciclovir	Empirical IV aciclovir started for possible HSV encephalitis is frequently continued for days after a negative CSF PCR obtained beyond 72 hours with an alternative diagnosis established. A hard prompt at 48–72 hours is high yield.
Standardised CMV pre-emptive thresholds	Centre-specific, assay-specific DNAemia thresholds for initiating and stopping pre-emptive therapy prevent both over-treatment of self-limiting low-level DNAemia and late initiation.
Mandatory renal dose-check and ideal-body-weight calculation for aciclovir	Directly prevents the commonest antiviral adverse event in the hospital.
Pharmacist-led interaction screening for every boosted or long-acting regimen	The highest-yield single intervention in HIV inpatient care; ritonavir/cobicistat with inhaled or intra-articular corticosteroids causing iatrogenic Cushing syndrome and adrenal suppression is both common and entirely preventable.
IV-to-oral switch protocols	Valaciclovir and valganciclovir achieve exposures adequate for most non-CNS, non-ocular indications A-I.
Respiratory virus panel stewardship	A positive rhinovirus or seasonal coronavirus PCR should stop antibacterials, not start antivirals. Report design — which organisms are reported and how — changes prescribing more than education does.
De-labelling "antiviral allergy"	Rare but obstructive; most reported aciclovir reactions are infusion-related or toxicity-related, not allergic.
Audit of treatment of asymptomatic viraemia	Urinary BK, low-level whole-blood EBV, and plasma HHV-6 DNAemia in HCT recipients are the three most frequently and least appropriately treated findings in transplant virology.

7.4 Specific overuse patterns worth naming

HHV-6 DNAemia. Detected in a large minority of HCT recipients, and in roughly 1% of the population it reflects **chromosomally integrated HHV-6 (ciHHV-6)**, present in every nucleated cell and producing persistently high, treatment-unresponsive "viral loads". Suspect ciHHV-6 when whole-blood HHV-6 DNA exceeds roughly $10^{5.5}$–10^{6} copies/mL and does not change with therapy; confirm by testing hair follicles or nails, or by a DNA copy-number ratio. Treating ciHHV-6 with ganciclovir or foscarnet is pure toxicity E-II.

Urinary BK. Treating BK viruria without DNAemia or biopsy-proven nephropathy. The primary intervention in BK nephropathy is **reduction of immunosuppression** A-II; cidofovir, leflunomide and IVIG have no convincing efficacy data C-III.

Respiratory viruses in the immunocompetent. Ribavirin for RSV and oral/aerosolised agents for parainfluenza in immunocompetent adults D-II.

Prolonged empirical aciclovir. See above.

Letermovir for established CMV disease. Its low genetic barrier and its being virostatic for packaging make it unsuitable as treatment D-II; it is a prophylactic agent.

Antivirals for EBV ``chronic fatigue''. Aciclovir and valganciclovir have no role E-II: they inhibit lytic replication, not the latent, episome-driven states that dominate EBV biology.

A SINGLE SENTENCE TO CARRY INTO EVERY ANTIVIRAL WARD ROUND

The commonest antiviral error is not choosing the wrong drug — it is treating a positive test in a patient who does not have the disease that test was ordered to find.

PART II

The human virome, virus by virus

8 Herpes simplex virus and varicella zoster virus

MOLECULAR VIROLOGY

HSV-1, HSV-2 and VZV are alphaherpesviruses: enveloped, icosahedral, linear dsDNA genomes of 152 kb (HSV) and 125 kb (VZV), replicating in the nucleus by a rolling-circle mechanism that generates head-to-tail concatemers, which are then cleaved to unit length and packaged by the terminase complex. Latency is established in sensory ganglia as a circularised episome with transcription restricted to the latency-associated transcript; **no antiviral acts on the latent genome**, which is the reason suppression is never cure.

Two viral enzymes carry the entire therapeutic edifice:

- **Thymidine kinase** (*UL23* in HSV, *ORF36* in VZV) — a promiscuous nucleoside kinase that monophosphorylates aciclovir, penciclovir and brivudine. Human TK1 does not.
- **DNA polymerase** (*UL30* in HSV, *ORF28* in VZV) — a B-family polymerase with 3′→5′ proofreading exonuclease, inhibited by the triphosphates of those drugs and, independently, by foscarnet and cidofovir.

Aciclovir triphosphate is an **obligate chain terminator** (the acyclic side chain has no 3′-OH) and additionally inactivates the polymerase in a dead-end complex when the next nucleotide binds — a "suicide" inhibition that contributes to its unusual potency. Selectivity is roughly 3 000-fold.

Alphaherpesvirus replication and the four points of attack FIGURE 8.1

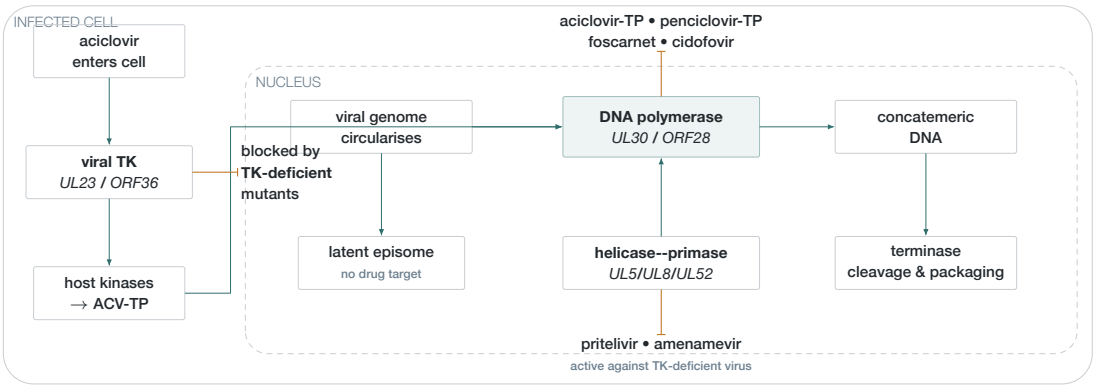


FIGURE 8.1. The dependence of aciclovir on a virus-encoded thymidine kinase is simultaneously the source of its safety and the source of its failure. Agents acting distal to the kinase — foscarnet, cidofovir — or on an entirely different enzyme — the helicase–primase inhibitors — retain activity against TK-deficient virus.

CLINICAL VIROLOGY — ASSAY & INTERPRETATION

- **Diagnosis** is by PCR on lesion swab, CSF, vitreous or tissue. Viral culture and DFA are obsolete for diagnosis but culture remains necessary for **phenotypic** susceptibility testing.
- **Type-specific serology** (gG1/gG2) answers a different question — prior infection — and has essentially no role in managing an acute lesion.
- **CSF HSV PCR may be negative in the first 72 hours** of encephalitis. A negative early result does not permit stopping aciclovir in a compatible syndrome; repeat at 3–7 days A-II.
- **Resistance testing** is genotypic (*UL23* and *UL30*) or phenotypic (PRA, the formal standard). Genotypic interpretation is harder here than for any other herpesvirus because *UL23* carries extensive natural polymorphism and because many resistance alleles are frameshifts in homopolymeric runs

— the G-strings at codons 146 and 430 are mutational hotspots. Approximately 95% of resistance is TK-mediated.

- **Who to test:** only patients with persistent or progressive lesions after ≥7–10 days of correctly dosed therapy, essentially always immunocompromised. Prevalence of aciclovir resistance is <1% in immunocompetent hosts and 4–10% in HCT recipients and advanced HIV.

BEDSIDE — REGIMEN, DOSE, MONITORING

Indication	Regimen	Evidence and notes
HSV encephalitis	Aciclovir IV 10 mg/kg q8h, 14–21 days	A-I. Dose on ideal body weight; hydrate. Repeat CSF PCR before stopping in children and the immunocompromised. Adjunctive corticosteroids remain unproven C-II. Consider **anti-NMDA-receptor encephalitis** in post-HSV relapse with movement disorder and psychiatric features — this is autoimmune, not viral relapse.
Neonatal HSV	Aciclovir IV 20 mg/kg q8h; 14 days (SEM) or 21 days (disseminated/CNS), then oral valaciclovir suppression for 6 months	A-I for both the acute course and the 6-month suppression, which improves neurodevelopmental outcome.
First-episode genital herpes	Valaciclovir 1 g bd ×7–10 days, or aciclovir 400 mg tds	A-I.
Recurrent genital herpes	Episodic valaciclovir 500 mg bd ×3 days, or suppressive valaciclovir 500 mg–1 g daily	A-I. Suppression reduces transmission to a susceptible partner by about half A-I.
Herpes labialis	Topical agents are marginal; oral valaciclovir 2 g bd for 1 day if started in prodrome	B-I.
Herpetic keratitis	Topical ganciclovir 0.15% gel or trifluridine; oral aciclovir for stromal disease with topical steroid under ophthalmology	A-I. **Never** give topical corticosteroid for dendritic epithelial keratitis.
Varicella (chickenpox), immunocompetent adult	Valaciclovir 1 g tds ×7 days, within 24 h of rash	B-II. Routine treatment of uncomplicated childhood varicella is not recommended D-I.
Varicella, immunocompromised or pneumonitis	Aciclovir IV 10 mg/kg q8h	A-II.
Herpes zoster	Valaciclovir 1 g tds ×7 days, or famciclovir 500 mg tds, started within 72 h	A-I. Benefit beyond 72 h is unproven except in ophthalmic, disseminated or immunocompromised disease. Corticosteroids improve acute pain but not postherpetic neuralgia C-I.
Herpes zoster ophthalmicus	Oral valaciclovir plus ophthalmology review	A-II.
Ramsay Hunt syndrome	Valaciclovir plus prednisolone	B-II.
VZV vasculopathy / CNS disease	Aciclovir IV 10–15 mg/kg q8h, 14 days, ± steroid	B-III.
Post-exposure prophylaxis (VZV)	VZIG within 10 days for susceptible high-risk contacts; otherwise aciclovir from day 7–14	A-II / B-II.

Aciclovir-resistant disease

- **First-line salvage: foscarnet** 40 mg/kg q8h or 60 mg/kg q12h IV A-II. Active because it needs no phosphorylation.
- **Second-line: cidofovir** IV with probenecid, or topical cidofovir 1% for localised cutaneous disease B-II.
- **Helicase–primase inhibitors** (pritelivir, amenamevir) are active against TK-deficient virus and are the most promising development in this area; pritelivir is available through expanded-access routes in several countries for refractory mucocutaneous HSV B-II.
- Remember that TK-deficient virus is attenuated: it causes chronic, indolent, enlarging mucocutaneous ulcers rather than fulminant disease, and reverts in the absence of drug pressure. **Immune reconstitution is the definitive treatment where it is achievable.**

9 Cytomegalovirus

MOLECULAR VIROLOGY

CMV (HHV-5) is a betaherpesvirus with a 236 kb genome, the largest of the human herpesviruses, encoding over 170 open reading frames of which a large fraction are devoted to immune evasion. Latency resides in $CD34^+$ myeloid progenitors and monocytes; reactivation accompanies myeloid differentiation and inflammation, which is why TNF-driven states, allogeneic transplantation and critical illness are its clinical settings.

Four gene products define its pharmacology:

UL97 A virus-encoded **protein kinase** (CMV has no thymidine kinase) that performs the first phosphorylation of ganciclovir. It also phosphorylates lamin A/C to permit nuclear egress — which is the actual target of **maribavir**, a benzimidazole riboside that inhibits the kinase rather than being activated by it.

UL54 The DNA polymerase; target of ganciclovir-TP, foscarnet and cidofovir.

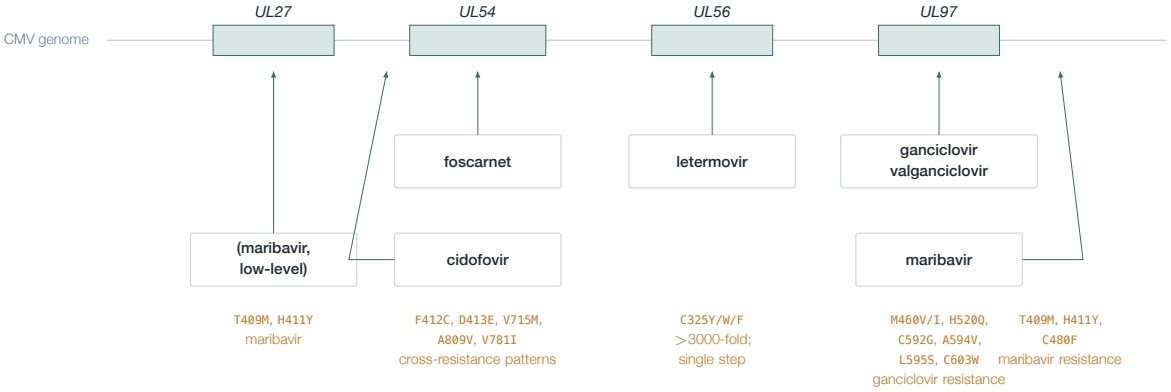
UL56, *UL89*, *UL51* The terminase complex, which cleaves concatemeric DNA into unit-length genomes and pumps them into preformed capsids. **Letermovir** binds pUL56. There is no human homologue of a terminase, which is why letermovir has essentially no myelotoxicity — the single most important property distinguishing it from ganciclovir.

UL27 Mutations here confer low-level maribavir resistance, probably by compensating for pUL97 inhibition.

THE CRUCIAL ANTAGONISM BETWEEN MARIBAVIR AND GANCICLOVIR

Ganciclovir *requires* pUL97 to be enzymatically active in order to be phosphorylated. Maribavir *inhibits* pUL97. The two are therefore mechanistically antagonistic *in vitro*, and should not be co-administered D-II.

CMV: drug targets and the genes that defeat them FIGURE 9.1



UL97 mutations affect ganciclovir only (foscarnet and cidofovir remain active). *UL54* mutations can affect ganciclovir, cidofovir and foscarnet in overlapping but non-identical patterns, and determine whether cross-resistance exists. *UL56* mutations affect letermovir alone. `C480F` in *UL97* confers maribavir resistance *and* ganciclovir cross-resistance.

FIGURE 9.1. Which gene is mutated determines which drugs remain available. This figure is the practical content of every CMV resistance report.

CLINICAL VIROLOGY — ASSAY & INTERPRETATION

- **Quantitative plasma PCR in IU/mL** is the monitoring standard. Whole blood runs 0.5–1 $\log_{10}$ higher; never switch matrix or platform mid-course A-II.
- **Thresholds are local.** There is no universal IU/mL trigger for pre-emptive therapy; each centre must define its own against its own assay, patient population and risk stratum A-II.
- **Tissue-invasive disease can occur with negative plasma DNAemia**, particularly gastrointestinal and retinal disease. Diagnosis of CMV colitis requires **histology with immunohistochemistry**, not stool or plasma PCR A-II.
- **CMV pneumonitis** requires BAL plus a compatible radiological and clinical picture; BAL PCR alone over-diagnoses, since shedding is common.
- **Resistance testing**: sequence *UL97* and *UL54* (and *UL56* if letermovir-exposed, *UL27* if maribavir-exposed). Request when DNAemia rises or plateaus after ≥2 weeks of adequately dosed therapy. Before that, resistance is unlikely and the answer is usually adherence, absorption, dose or immunosuppression.
- **CMV cell-mediated immunity assays** (QuantiFERON-CMV, ELISPOT) are increasingly used to stratify who can safely stop prophylaxis B-II.

BEDSIDE — REGIMEN, DOSE, MONITORING

Setting	Regimen	Evidence and notes
Prophylaxis, allogeneic HCT (seropositive recipient)	Letermovir 480 mg daily (240 mg with ciclosporin) from engraftment to day 100, extendable to day 200 in high-risk patients	A-I. Reduces clinically significant CMV infection and all-cause mortality. Extension to 200 days reduces late reactivation A-I.
Prophylaxis, solid organ transplant (D+/R−)	Valganciclovir 900 mg daily for 3–6 months (6 months in kidney, often 6–12 in lung)	A-I. Alternative: pre-emptive monitoring A-I — both strategies are acceptable; prophylaxis is preferred in D+/R− and in lung and intestinal transplantation.
Pre-emptive therapy	Valganciclovir 900 mg bd until DNAemia clears (usually 2 consecutive negatives)	A-I.
CMV disease, non-severe	Valganciclovir 900 mg bd	A-I, with the stated exceptions.
CMV disease, severe / CNS / unable to absorb	Ganciclovir IV 5 mg/kg q12h	A-I. Treat for at least 2–3 weeks *and* until DNAemia is cleared and symptoms resolve.
CMV retinitis	Systemic ganciclovir/valganciclovir *plus* intravitreal ganciclovir or foscarnet for immediate sight-threatening lesions	A-II. In HIV, start or optimise ART; expect immune recovery uveitis.
Resistant/refractory CMV	**Maribavir 400 mg bd** for refractory/resistant disease A-I (superior to investigator-assigned therapy for viraemia clearance); alternatives foscarnet A-II or cidofovir B-II	Maribavir does **not** reliably treat CNS or retinal disease (poor penetration) D-III and relapse with `T409M`/`H411Y`/`C480F` is common. High-dose ganciclovir is reasonable for a low-level *UL97* mutant with modest fold change C-III.
Congenital CMV, symptomatic	Valganciclovir 16 mg/kg bd ×6 months	A-I; improves hearing and neurodevelopment. Not indicated for asymptomatic infection D-I.
CMV-specific T cells (VSTs)	Third-party or donor-derived	B-II for refractory disease where available.

Toxicity: the practical burden

Ganciclovir and valganciclovir cause dose-limiting **neutropenia** (up to 30%), thrombocytopenia and anaemia; monitor FBC at least twice weekly during induction. When the virus is still replicating, **add G-CSF rather than reduce the dose** B-II — dose reduction in the face of active replication is the classic route to selecting *UL97* mutants. Foscarnet causes nephrotoxicity and severe electrolyte wasting (calcium, magnesium, potassium, phosphate) with seizures from acute ionised hypocalcaemia; genital ulceration is characteristic. Cidofovir's nephrotoxicity is dose-limiting and partly irreversible; probenecid and saline loading are mandatory. Maribavir's dominant adverse effect is **dysgeusia** (a metallic taste) in roughly half of patients, which is tolerable but affects adherence; it also raises tacrolimus levels.

10 Epstein--Barr virus, HHV-6, HHV-7 and HHV-8

10.1 Epstein--Barr virus (HHV-4)

MOLECULAR VIROLOGY

A gammaherpesvirus establishing lifelong latency in memory B cells. Its oncogenic programmes (latency I, II and III) are driven by EBNA and LMP proteins expressed from a circular episome replicated by **host** DNA polymerase during cell division. This is the decisive pharmacological fact: **aciclovir, ganciclovir and all polymerase inhibitors act only on lytic replication and have no effect whatever on latent, proliferating, EBV-driven malignancy or lymphoproliferative disease** E-II.

CLINICAL VIROLOGY — ASSAY & INTERPRETATION

Quantitative EBV DNA (whole blood or plasma; plasma correlates better with PTLD). Serology (VCA IgM/IgG, EBNA-1 IgG) distinguishes acute from past infection. A rising plasma EBV DNA in a transplant recipient is the trigger for intervention, though thresholds are centre-specific.

BEDSIDE — REGIMEN, DOSE, MONITORING

- **Infectious mononucleosis:** supportive care. Aciclovir reduces oropharyngeal shedding but not symptoms D-I. Corticosteroids only for airway compromise C-III.
- **Post-transplant lymphoproliferative disorder: reduction of immunosuppression** first A-II, then rituximab A-II, then chemotherapy; EBV-specific cytotoxic T lymphocytes for refractory disease B-II. Antivirals have no established role D-II.
- **Chronic active EBV, HLH:** immunochemotherapy and allogeneic HCT; antivirals ineffective D-III.
- **Oral hairy leukoplakia:** a genuinely lytic lesion — responds to high-dose aciclovir or valaciclovir B-II, but ART is the real treatment.
- **Nasopharyngeal carcinoma, Burkitt and Hodgkin lymphoma:** oncological management; plasma EBV DNA is a validated biomarker in nasopharyngeal carcinoma.

10.2 HHV-6A, HHV-6B and HHV-7

MOLECULAR VIROLOGY

Betaherpesviruses, tropic for $CD4^+$ T cells; HHV-6B uses CD134 (OX40) as receptor and causes roseola infantum. Both encode a *U69* protein kinase homologous to CMV pUL97 — hence ganciclovir activity — and a *U38* DNA polymerase. **HHV-6 uniquely integrates into host telomeres**; in roughly 1% of people this is inherited through the germline as **chromosomally integrated HHV-6 (ciHHV-6)**, present at one copy per nucleated cell.

CLINICAL VIROLOGY — ASSAY & INTERPRETATION

This is the one scenario where a very high viral load means *less* rather than more. Suspect ciHHV-6 when whole-blood HHV-6 DNA is persistently $>10^{5.5}$–10^6 copies/mL, is unchanged by therapy, and is present in a healthy relative. Confirm by hair follicle or nail testing, or by digital PCR showing a viral:cellular genome ratio near 1. Testing for ciHHV-6 before committing a patient to weeks of foscarnet is one of the highest-value interventions in transplant virology.

BEDSIDE — REGIMEN, DOSE, MONITORING

- **HHV-6 encephalitis (post-transplant limbic encephalitis):** the only firm indication. Foscarnet or ganciclovir, often in combination, 3 weeks B-II. HHV-6A/B is intrinsically *resistant to aciclovir*.
- **HHV-6 DNAemia without disease:** do not treat D-II.
- **ciHHV-6:** do not treat E-II.
- **Roseola, DRESS-associated reactivation:** supportive; stop the culprit drug.
- **HHV-7:** no established antiviral indication C-III.

10.3 HHV-8 (Kaposi sarcoma-associated herpesvirus)

MOLECULAR VIROLOGY

A gammaherpesvirus causing Kaposi sarcoma, primary effusion lymphoma, multicentric Castleman disease and KSHV inflammatory cytokine syndrome. As with EBV, the pathology is driven by **latent** gene expression (LANA, vCyclin, vFLIP, vIL-6), which polymerase inhibitors do not touch. However, MCD and KICS have a substantial **lytic** component, and here antivirals do contribute.

BEDSIDE — REGIMEN, DOSE, MONITORING

- **Kaposi sarcoma:** ART is the primary treatment in HIV-associated disease A-I; chemotherapy (liposomal anthracyclines, paclitaxel) for advanced or visceral disease. Antivirals do not treat established KS D-II, though ganciclovir prophylaxis reduces *incident* KS B-II.
- **Multicentric Castleman disease:** rituximab ± chemotherapy A-II; adjunctive ganciclovir or valganciclovir with zidovudine is used in severe disease B-III.
- **Primary effusion lymphoma:** chemotherapy; prognosis poor.

10.4 B virus (Macacine alphaherpesvirus 1)

A zoonotic alphaherpesvirus of macaques causing rapidly fatal human encephalomyelitis after bites, scratches or mucosal exposure. **Post-exposure prophylaxis with valaciclovir 1 g q8h for 14 days** is recommended after high-risk exposure B-III; established disease is treated with intravenous aciclovir or ganciclovir B-III. Mortality without treatment approaches 70%. This is an emergency that depends almost entirely on recognising the exposure history.

11 Hepatitis B and hepatitis D

MOLECULAR VIROLOGY

HBV is the only human Baltimore class VII virus: a 3.2 kb partially double-stranded relaxed circular DNA genome that replicates *through an RNA intermediate* using a virus-encoded reverse transcriptase with RNase H activity. Four overlapping reading frames (*P*, *S*, *C*, *X*) are packed into that genome, so a mutation in one necessarily alters another — the structural reason that polymerase resistance mutations generate surface-antigen variants.

The therapeutic problem is **covalently closed circular DNA (cccDNA)**: on entry via the bile acid transporter **NTCP (SLC10A1)**, relaxed circular DNA is repaired in the nucleus into a stable minichromosome that serves as the transcriptional template. cccDNA has a long half-life, is replenished by intracellular recycling, is not a substrate for any licensed antiviral, and persists after HBsAg loss. Integrated HBV DNA additionally produces HBsAg independently of replication. **Nucleos(t)ide analogues suppress reverse transcription; they do not eliminate the template.** Everything clinically distinctive about HBV therapy follows from that sentence.

The HBV replication cycle and why suppression is not cure FIGURE 11.1

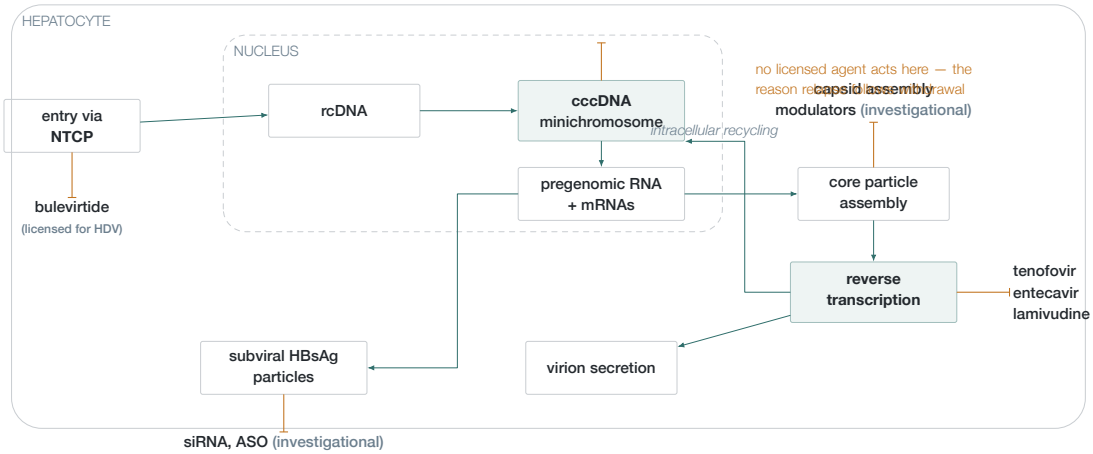


FIGURE 11.1. Licensed therapy inhibits reverse transcription only. cccDNA is replenished by intracellular recycling and is untouched, so viraemia returns when the drug stops. Investigational agents target entry, capsid assembly and HBsAg output in pursuit of functional cure.

CLINICAL VIROLOGY — ASSAY & INTERPRETATION

Marker	Interpretation
HBsAg	Current infection (>6 months = chronic). Loss, with or without anti-HBs, defines **functional cure**.
Anti-HBs	Immunity (vaccination or resolved infection).
Anti-HBc total	Exposure. **Isolated anti-HBc** may be occult infection, resolved infection with waned anti-HBs, or false positive — and marks genuine risk of reactivation under immunosuppression.
HBeAg / anti-HBe	Historically a marker of high replication; **precore (`G1896A`) and basal core promoter (`A1762T/G1764A`) variants** produce HBeAg-negative disease with high DNA and active hepatitis — do not equate HBeAg-negative with inactive.
HBV DNA (IU/mL)	The replication measure driving treatment decisions.
Quantitative HBsAg	Used to characterise the inactive carrier state and to predict response; increasingly used as an endpoint in novel-agent trials.
HDV RNA, anti-HDV	Test **every** HBsAg-positive patient at least once for hepatitis D A-I — it is widely under-diagnosed and is the most aggressive chronic viral hepatitis.

BEDSIDE — REGIMEN, DOSE, MONITORING

Who to treat

Treat if cirrhosis and any detectable HBV DNA A-I; if HBV DNA >2 000 IU/mL with raised ALT or significant fibrosis A-I; in pregnancy with DNA >200 000 IU/mL from week 24–28 to prevent transmission A-I; in anyone receiving B-cell-depleting therapy, anthracyclines, or significant corticosteroid courses as **reactivation prophylaxis** A-I; and in extrahepatic disease such as polyarteritis nodosa or glomerulonephritis B-II.

Agents

Agent	Dose	Position
Tenofovir disoproxil fumarate	245 mg daily	First line A-I. No established resistance after a decade. Monitor renal function and bone.
Tenofovir alafenamide	25 mg daily	First line A-I; preferred with renal impairment, osteoporosis, or age >60. Dyslipidaemia is more frequent than with TDF.
Entecavir	0.5 mg daily (nucleoside-naive)	First line in naive patients A-I. **1 mg daily and a collapsed resistance barrier if lamivudine-experienced** — do not use avoid after 3TC.
Lamivudine, telbivudine, adefovir	—	**Obsolete** as monotherapy D-I: unacceptable resistance rates.
Peginterferon alfa-2a	180 μg weekly ×48 weeks	Finite course, possibility of HBsAg loss, no resistance — but poorly tolerated and contraindicated in decompensated cirrhosis B-I.
Bulevirtide	2 mg SC daily	**For HDV** A-I. Blocks NTCP-mediated entry; causes asymptomatic bile-salt elevation. Optimal duration undefined.

Stopping, and the hazard of stopping

Nucleos(t)ide therapy is generally lifelong in cirrhosis A-I. In non-cirrhotic HBeAg-positive patients, consolidation for 12 months after HBeAg seroconversion may permit withdrawal B-II. **Severe hepatitis flares, including hepatic decompensation and death, follow abrupt withdrawal** — never stop without a monitoring plan withdrawal flare.

Reactivation prophylaxis

In HBsAg-positive patients receiving rituximab or equivalent, prophylaxis is mandatory A-I and should continue for at least 12 months after the last dose. In HBsAg-negative, anti-HBc-positive patients receiving B-cell-depleting therapy, prophylaxis is also recommended A-II; for lower-risk immunosuppression, DNA monitoring with pre-emptive therapy is acceptable B-II.

11.1 Hepatitis D

A defective satellite RNA agent (1.7 kb circular, rod-like, ribozyme-containing) requiring HBsAg for its envelope. It encodes only the small and large delta antigens and uses **host** RNA polymerase II — there is no viral polymerase to inhibit, which is why nucleos(t)ide analogues have no activity against HDV E-I and why the only successful strategies are entry inhibition (bulevirtide) and interferon. Coinfection accelerates fibrosis and raises hepatocellular carcinoma risk severalfold. Treat with bulevirtide 2 mg daily A-I, ± peginterferon alfa B-II, continuing HBV nucleos(t)ide therapy as indicated.

12 Hepatitis C

MOLECULAR VIROLOGY

A 9.6 kb positive-sense RNA flavivirus translated as a single polyprotein, cleaved by host signal peptidase and two viral proteases (NS2 autoprotease, NS3/4A serine protease) into ten products. Three are drugged.

The HCV polyprotein and the three direct-acting antiviral classes FIGURE 12.1

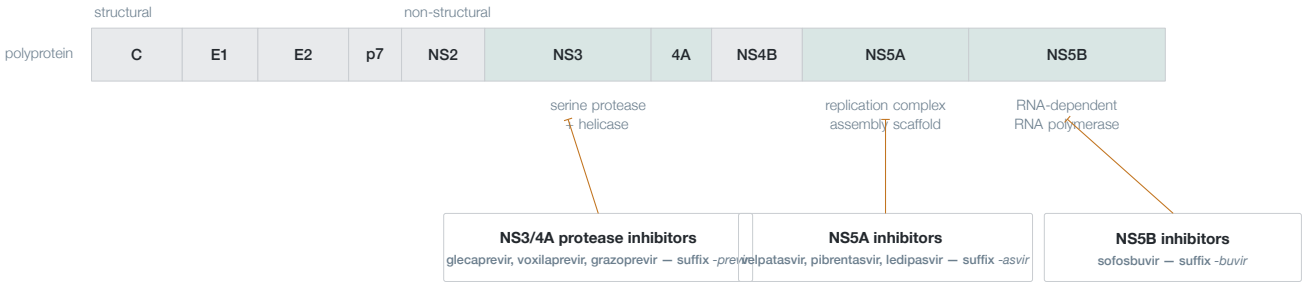


FIGURE 12.1. The international nonproprietary name suffix identifies the target: *-previr* for the NS3/4A protease, *-asvir* for NS5A, *-buvir* for NS5B. Every licensed pangenotypic regimen is a combination of two of these three classes.

CLINICAL VIROLOGY — ASSAY & INTERPRETATION

Diagnosis is anti-HCV antibody followed by **HCV RNA** to confirm viraemia; a positive antibody with undetectable RNA indicates cleared or treated infection. HCV core antigen is an acceptable alternative where RNA testing is unavailable B-II. **Genotyping is now largely unnecessary** with pangenotypic regimens A-I. Baseline resistance testing is not routinely required; NS5A RAS testing (notably `Y93H`, `L31M`) is reserved for retreatment after DAA failure B-II. The cure endpoint is **SVR12** — undetectable RNA 12 weeks after completing therapy, which is durable in >99%.

BEDSIDE — REGIMEN, DOSE, MONITORING

Regimen	Duration	Position
Sofosbuvir/velpatasvir	12 weeks	Pangenotypic first line A-I. Safe in decompensated cirrhosis (add ribavirin) because it contains no protease inhibitor.
Glecaprevir/pibrentasvir	8 weeks (treatment-naive, no cirrhosis or compensated cirrhosis)	Pangenotypic first line A-I. **Contraindicated in Child–Pugh B/C** E-I.
Sofosbuvir/velpatasvir/voxilaprevir	12 weeks	Salvage after DAA failure A-I. Contraindicated in decompensated cirrhosis.
Ribavirin	—	Adjunct only, in decompensated cirrhosis or difficult retreatment. Teratogenic E-II; haemolytic anaemia.

THREE THINGS THAT ARE EASY TO GET WRONG IN HCV

1. HBV reactivation. DAAs can precipitate HBV reactivation, including fulminant hepatitis. Screen every patient for HBsAg and anti-HBc before starting, and treat or monitor accordingly A-II. **2. Interactions.** Protease-inhibitor-containing DAAs interact extensively; amiodarone with sofosbuvir causes symptomatic bradycardia and is contraindicated E-II. Acid-suppressing drugs reduce ledipasvir and velpatasvir absorption. **3. Cure is not discharge.** Patients with cirrhosis require lifelong 6-monthly hepatocellular carcinoma surveillance after SVR A-II, and reinfection is possible in those with ongoing exposure — SVR confers no immunity.

13 Hepatitis A and hepatitis E

13.1 Hepatitis A

A non-enveloped picornavirus (*Hepatovirus A*) transmitted faecal–orally, causing acute hepatitis that does not become chronic. **There is no antiviral therapy and none is needed** E-III; management is supportive, with transplantation for the rare fulminant case. The clinically important interventions are preventive: inactivated vaccine, and post-exposure prophylaxis with vaccine (preferred, within 14 days) or immunoglobulin in infants under 12 months, the immunocompromised and those with chronic liver disease A-I. Outbreaks among people who are homeless or who inject drugs are the dominant modern epidemiology.

13.2 Hepatitis E

A quasi-enveloped positive-sense RNA hepevirus. Genotypes 1 and 2 are human, waterborne, and cause large epidemics with **mortality up to 20–25% in the third trimester of pregnancy**. Genotypes 3 and 4 are zoonotic (pigs, deer, shellfish), food-borne, endemic in high-income countries, and are the genotypes that cause **chronic infection in the immunosuppressed**, progressing to cirrhosis over months to a few years.

MOLECULAR VIROLOGY

An ORF1 polyprotein encodes methyltransferase, helicase and RdRp. Ribavirin's activity is attributed to RdRp inhibition, lethal mutagenesis and GTP-pool depletion. The `G1634R` substitution in the RdRp is associated with reduced ribavirin response.

CLINICAL VIROLOGY — ASSAY & INTERPRETATION

Serology performs poorly in the immunosuppressed; **diagnose chronic HEV by serum and stool HEV RNA**, not antibody A-II. Any transplant recipient with unexplained chronic transaminitis should have HEV RNA tested — it is routinely missed and is a reversible cause of graft hepatitis.

BEDSIDE — REGIMEN, DOSE, MONITORING

- **Acute HEV, immunocompetent:** supportive A-III.
- **Chronic HEV in transplant: first reduce immunosuppression** — this alone clears roughly a third A-II. If RNA persists at 3 months, **ribavirin monotherapy** 600–800 mg daily (weight- and haemoglobin-adjusted) for 3 months, extended to 6 months if RNA remains detectable at 3 months B-II. Check RNA in serum *and stool* at the end of therapy — stool clearance lags and predicts relapse.
- **Severe acute HEV or acute-on-chronic liver failure:** ribavirin is used C-III.
- **Pregnancy:** ribavirin is contraindicated E-II; management is supportive.
- Peginterferon has been used in liver transplant recipients C-III but carries rejection risk in other organ transplants.

14 Human immunodeficiency virus

MOLECULAR VIROLOGY

HIV-1 is a lentivirus with two copies of a 9.7 kb positive-sense RNA genome. Entry requires sequential engagement of CD4 and a chemokine coreceptor (CCR5 or CXCR4) by gp120, followed by gp41-mediated six-helix-bundle formation and fusion. Reverse transcriptase — which has **no proofreading** — produces double-stranded DNA that is imported into the nucleus within an intact or partially intact capsid, then integrated by integrase. The provirus is transcribed by host machinery; Gag and Gag-Pol polyproteins assemble at the membrane and are cleaved by the viral protease during maturation.

Two properties dominate therapy:

- **Mutation supply is effectively infinite.** With $\sim 10^{10}$ virions per day and an error rate near 10^{-4}–10^{-5}, every single mutant and most double mutants pre-exist before the first dose. **Monotherapy fails by arithmetic** E-I.
- **The latent reservoir** of integrated, transcriptionally silent provirus in resting memory $CD4^+$ T cells is established within days of infection, has a half-life of roughly 44 months, and is invisible to every antiretroviral. This is why ART is lifelong and why "cure" remains confined to a handful of cases of allogeneic transplantation with CCR5-Δ32 donors.

HIV replication and the seven antiretroviral target classes FIGURE 14.1

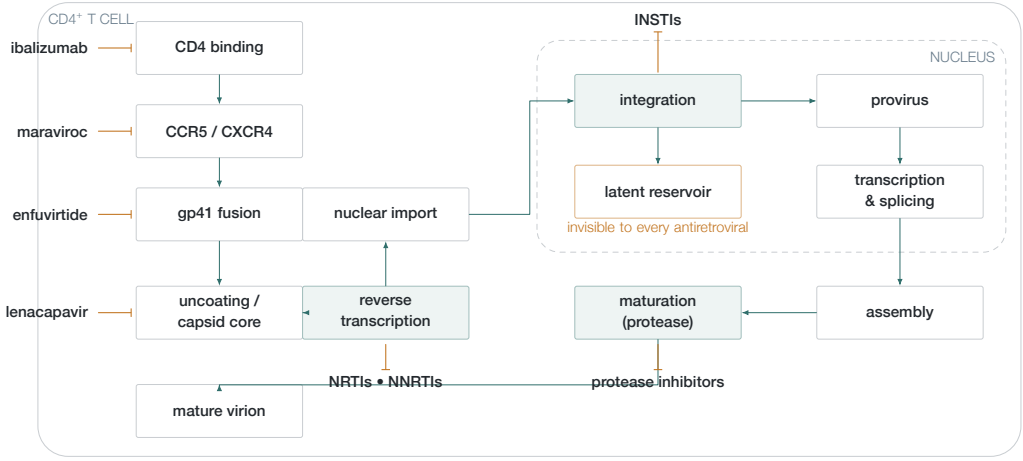


FIGURE 14.1. Lenacapavir is unique in acting at several stages, because the capsid participates in uncoating, nuclear import and maturation. No agent acts on the latent provirus.

CLINICAL VIROLOGY — ASSAY & INTERPRETATION

- **Diagnosis:** fourth-generation antigen/antibody immunoassay, confirmed by an antibody differentiation assay; HIV RNA for acute infection before seroconversion and for infants. **Infant diagnosis requires HIV DNA or RNA PCR**, not serology, because of transplacental maternal antibody.
- **Monitoring:** plasma HIV-1 RNA and CD4 count. Suppression is <50 copies/mL. Blips are common and not failure; confirmed >200 copies/mL is failure A-I.
- **Resistance testing:** baseline genotype (protease/RT) for everyone entering care A-II; **integrase genotype must be requested separately** and is indicated at baseline where transmitted INSTI resistance is a concern and always at INSTI failure A-III. Test **on therapy or within 4 weeks of stopping** A-II. Proviral DNA genotyping is an option in suppressed patients needing a regimen change, with the caveat that it over-calls resistance from defective genomes.

- **Tropism testing** before maraviroc: genotypic V3-loop analysis with geno2pheno (FPR cut-off ~10%) or phenotypic assay A-I.
- **HLA-B*57:01** must be negative before abacavir A-I.

BEDSIDE — REGIMEN, DOSE, MONITORING

First-line therapy

Regimen	Comment
Bictegravir/emtricitabine/TAF	Single tablet, high barrier, few interactions A-I.
Dolutegravir + TAF or TDF/XTC	A-I; dolutegravir is recommended in pregnancy and at conception A-II.
Dolutegravir/lamivudine	Two-drug first line in eligible patients: HIV RNA <500 000 copies/mL, HBsAg-negative, no baseline resistance and baseline genotype available A-I.
Doravirine-based	Useful alternative with a favourable lipid and interaction profile B-I.
Cabotegravir/rilpivirine IM	Long-acting maintenance in virologically suppressed patients without resistance to either class and without HBV coinfection A-I.

Key resistance pathways

Class	Signature substitutions	Clinical meaning
NRTI	`M184V/I`	Confers high-level 3TC/FTC resistance but *reduces* replication capacity and *resensitises* to zidovudine and tenofovir. Often worth retaining 3TC/FTC for this reason B-II.
NRTI	TAMs: `M41L`, `D67N`, `K70R`, `L210W`, `T215Y/F`, `K219Q/E`	Excision-based; accumulate stepwise; cause broad NRTI cross-resistance.
NRTI	`K65R`	Tenofovir, abacavir; antagonistic with TAMs.
NRTI	`Q151M` complex, `T69` insertions	Multi-NRTI resistance; rare but severe.
NNRTI	`K103N`, `Y181C`, `G190A`, `E138K`	Single-step, low fitness cost, archived for years. `K103N` spares etravirine; `Y181C` compromises it.
INSTI	`Q148H/R/K` + `G140S`, `N155H`, `Y143R`	First-generation (raltegravir, elvitegravir) pathways; `Q148` plus secondary mutations is the pathway that also compromises dolutegravir.
INSTI	`R263K`, `G118R`	Second-generation pathway; uncommon, high fitness cost.
PI	Accumulating `I50V`, `I54M`, `L76V`, `I84V`, `V82A`	Boosted darunavir requires several; failure usually means non-adherence, not resistance.
Capsid	`M66I`, `N74D`, `Q67H`	Lenacapavir; relevant in heavily treatment-experienced patients.

Prevention

- **PrEP:** daily TDF/FTC A-I; TAF/FTC A-I (not for receptive vaginal exposure — no efficacy data); on-demand "2-1-1" TDF/FTC for men who have sex with men A-I; long-acting injectable cabotegravir 2-monthly A-I; and lenacapavir 6-monthly, which has shown exceptional efficacy A-I. **Exclude acute HIV before starting any PrEP** — initiating PrEP during acute infection selects resistance.
- **PEP:** 28 days of tenofovir/emtricitabine plus dolutegravir or raltegravir, started as soon as possible and within 72 hours A-II.
- **Prevention of vertical transmission:** maternal ART with suppression, with infant prophylaxis stratified by risk A-I.
- **U=U:** sustained suppression below 200 copies/mL means HIV is not transmitted sexually A-I.

The pharmacokinetic tail

Long-acting cabotegravir and lenacapavir persist at declining, subtherapeutic concentrations for months after the last injection. If therapy is stopped without an oral bridging regimen, the patient is effectively on declining monotherapy and integrase or capsid resistance can be selected always bridge orally.

14.1 HIV-2

Intrinsically **resistant to all NNRTIs** E-II and to enfuvirtide, and has reduced susceptibility to some protease inhibitors (use darunavir, lopinavir or saquinavir). Treat with two NRTIs plus an integrase inhibitor or boosted darunavir B-II. Viral load assays must be HIV-2-specific; an HIV-1 RNA assay will read undetectable in an untreated HIV-2 infection.

14.2 HTLV-1 and HTLV-2

A deltaretrovirus causing adult T-cell leukaemia/lymphoma and HTLV-1-associated myelopathy/tropical spastic paraparesis, plus infective dermatitis and an association with *Strongyloides* hyperinfection. Transmission is largely cell-to-cell, and proviral load rather than free virus drives disease. **There is no effective antiviral therapy** C-III. Zidovudine plus interferon alfa is used in leukaemic and smouldering ATL subtypes with reasonable evidence B-II but not in the lymphoma subtype, which is treated with chemotherapy. Antiretrovirals used for HIV do not reduce HTLV proviral load D-II. Screening of blood donors and avoidance of breastfeeding where alternatives are safe are the effective interventions A-II.

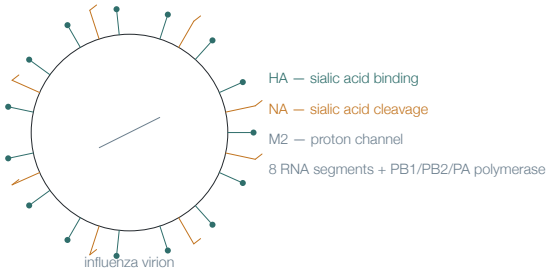
15 Influenza

MOLECULAR VIROLOGY

A segmented, negative-sense RNA orthomyxovirus: eight segments in influenza A and B, seven in influenza C. Three features define its pharmacology and its epidemiology.

1. **Cap-snatching.** Influenza cannot cap its own mRNA. The polymerase heterotrimer (PB1, PB2, PA) binds host pre-mRNA via PB2, and the **PA endonuclease** cleaves 10–13 nucleotides downstream of the cap to prime viral transcription. **Baloxavir** inhibits this endonuclease by chelating its two active-site metal ions — a mechanism with no human counterpart.
2. **Receptor destruction.** Haemagglutinin binds sialic acid; neuraminidase cleaves it, releasing progeny and preventing self-aggregation. **Neuraminidase inhibitors** are sialic-acid transition-state analogues.
3. **Segmentation permits reassortment**, producing antigenic shift and the possibility of abrupt pandemic emergence — and, equally, abrupt acquisition of a resistance-bearing segment.

Influenza: three drugged steps and the resistance substitution at each FIGURE 15.1



M2 ion channel

amantadine, rimantadine. Blocks acidification and uncoating; influenza A only.

`S31N` fixed in all circulating seasonal A — obsolete

Neuraminidase

oseltamivir, zanamivir, peramivir, laninamivir. Prevents release of progeny.

`H275Y` (N1, oseltamivir/peramivir; zanamivir retained); `R292K`, `E119V` (N2)

PA endonuclease

baloxavir marboxil. Blocks cap-snatching; single oral dose.

`I38T/M/F`: 2–10% of treated adults, up to 20–25% of treated children

FIGURE 15.1. Oseltamivir resistance is subtype- and agent-specific: `H275Y` in N1 abolishes oseltamivir and peramivir activity while leaving zanamivir intact, because zanamivir's structure does not depend on the hydrophobic pocket that `H275Y` distorts.

CLINICAL VIROLOGY — ASSAY & INTERPRETATION

- **RT-PCR** on nasopharyngeal swab is the diagnostic standard; rapid antigen tests have poor and variable sensitivity and a negative result does not exclude influenza in a compatible illness during a season A-II.
- **In severe or immunocompromised disease, sample the lower tract** — upper airway specimens can be negative while BAL is positive.
- **Phenotypic susceptibility** is measured by the fluorescent MUNANA neuraminidase inhibition assay, reported as *reduced* or *highly reduced inhibition* rather than "resistant". **This assay cannot detect baloxavir or M2 resistance**; those require sequencing of *PA* and *M2*.
- **When to test for resistance:** clinical deterioration or persistent viral shedding on therapy, particularly in immunocompromised patients, and in anyone who develops influenza while receiving prophylaxis.

BEDSIDE — REGIMEN, DOSE, MONITORING

Setting	Regimen	Evidence
Uncomplicated influenza, high-risk or early presentation	Oseltamivir 75 mg bd ×5 days, or baloxavir 40–80 mg single dose	A-I within 48 h. Benefit is greatest the earlier it is given; in outpatients the effect on symptom duration is roughly one day, with reduction in lower-respiratory complications in high-risk groups.
Hospitalised or severe influenza	Oseltamivir 75 mg bd, start regardless of time since onset, 5 days, extended if still shedding	A-II (observational; no RCT in severe disease). **Dose doubling is not beneficial** D-I.
Critically ill, unable to absorb enterally	Peramivir IV 600 mg, or zanamivir IV where available	B-II.
Immunocompromised	Oseltamivir, extended duration, with resistance surveillance	B-III. **Avoid baloxavir monotherapy** in prolonged shedding because of rapid `I38T` emergence C-III.
Post-exposure prophylaxis	Oseltamivir 75 mg daily ×7–10 days, or baloxavir single dose	A-I in high-risk contacts and institutional outbreaks.
Pregnancy	Oseltamivir, treat promptly	A-II.
Zoonotic / avian influenza (H5N1, H7N9)	Oseltamivir, often at extended duration; consider combination	B-III. Most avian strains remain M2-resistant and NAI-susceptible, but confirm with reference laboratory testing.

TWO PRACTICE POINTS THAT ARE FREQUENTLY GOT WRONG

Baloxavir and dairy. Polyvalent cations (calcium, magnesium, aluminium, iron) chelate baloxavir and substantially reduce absorption. Avoid dairy products, antacids and mineral supplements around dosing. **Combination therapy.** Baloxavir plus a neuraminidase inhibitor has not shown clinical superiority over monotherapy in trials C-I, although it is reasonable in the immunocompromised with prolonged shedding on mechanistic grounds C-III.

16 Coronaviruses

MOLECULAR VIROLOGY

Coronaviruses have the largest known RNA genomes (27–32 kb), which is only possible because **nsp14 encodes a 3′→5′ exoribonuclease (ExoN)** that proofreads nsp12 RdRp. This single fact explains much of coronavirus pharmacology: nucleoside analogues are partially excised, so potency is lower than it would otherwise be, and the barrier to mutagenic agents is raised. The replicase polyproteins pp1a/pp1ab are processed by two proteases: the papain-like protease (nsp3) and the **main protease M^{pro} (3CL protease, nsp5)**, which cleaves at eleven sites and has a catalytic Cys145–His41 dyad with a strict glutamine requirement at P1 — a specificity unmatched by any human protease, and the structural basis of nirmatrelvir's selectivity.

Seven human coronaviruses: four endemic (229E, OC43, NL63, HKU1) causing common colds and, in the frail, lower respiratory disease; and three epidemic/pandemic (SARS-CoV, MERS-CoV, SARS-CoV-2).

BEDSIDE — REGIMEN, DOSE, MONITORING

SARS-CoV-2

Agent	Regimen	Position
Nirmatrelvir/ritonavir	300/100 mg bd ×5 days, within 5 days of onset	First-line oral therapy for high-risk outpatients A-I. Renal dose reduction at eGFR 30–60; contraindicated below 30. **The ritonavir component drives an enormous interaction burden** — review every medicine, particularly calcineurin inhibitors, anticoagulants, statins, antiarrhythmics and antiepileptics.
Remdesivir	200 mg then 100 mg daily; 3 days for outpatients, 5–10 days for inpatients	A-I outpatient; A-I in hospitalised patients requiring supplemental oxygen but not mechanical ventilation. Benefit is less clear once mechanical ventilation is established C-I.
Molnupiravir	800 mg bd ×5 days	Reserve for when neither of the above can be used C-I: efficacy is lower, and the mutagenic mechanism raises both individual (contraindicated in pregnancy E-III) and population-level concerns.
Monoclonal antibodies	—	Successive agents have been rendered obsolete by spike evolution. **Never use a mAb without current local variant susceptibility data** A-II.
Dexamethasone and immunomodulators	6 mg daily; tocilizumab or baricitinib	A-I in hypoxaemic patients. **Corticosteroids are harmful in non-hypoxaemic disease** D-I. Note the conceptual division: antivirals work early, immunomodulators work late, and giving either at the wrong phase is ineffective or harmful.

Prolonged infection in the immunocompromised

B-cell-depleted patients can shed replication-competent virus for months, with intrahost evolution that has repeatedly seeded new variant lineages. Prolonged or combination antiviral therapy, sometimes with an active monoclonal antibody and convalescent plasma, is used C-III; there are no randomised data. This population is also where `nsp5 E166V` and remdesivir-associated `nsp12 V792I`/`E802D` substitutions have been documented.

MERS-CoV

Case fatality approaching 35%; dromedary camel reservoir. No licensed antiviral. Remdesivir and interferon-β1b with lopinavir/ritonavir have been studied C-II. Management is supportive with rigorous infection control, since nosocomial amplification dominates the epidemiology.

Endemic human coronaviruses

No antiviral therapy is indicated E-III. Their clinical importance is as a cause of positive multiplex panels that should prompt antibacterial de-escalation rather than antiviral initiation.

17 Respiratory syncytial virus, metapneumovirus and the parainfluenza viruses

17.1 Respiratory syncytial virus

MOLECULAR VIROLOGY

A pneumovirus with a non-segmented negative-sense RNA genome. The **fusion (F) glycoprotein** exists in a metastable prefusion conformation that refolds irreversibly into the postfusion state to drive membrane fusion. The dominant neutralising epitope, **site Ø**, exists only on prefusion F. Stabilising prefusion F was the structural insight that produced both the effective monoclonal antibodies and the maternal vaccine, after decades of failure — including the 1960s formalin-inactivated vaccine that caused enhanced disease.

BEDSIDE — REGIMEN, DOSE, MONITORING

Intervention	Regimen	Position
Nirsevimab	Single IM dose, all infants entering their first season	A-I. An extended-half-life prefusion-F monoclonal antibody — immunoprophylaxis, not a vaccine. Has transformed infant RSV epidemiology.
Palivizumab	Monthly IM through the season, restricted high-risk infants	A-I, now largely superseded by nirsevimab.
Maternal RSVpreF vaccine	24–36 weeks' gestation	A-I.
Older-adult RSV vaccines	Single dose from age 60–75 depending on programme	A-I.
Ribavirin (aerosolised or oral)	—	**Not recommended in immunocompetent infants** D-I. In HCT recipients with lower respiratory tract disease it is widely used with IVIG C-II, but the evidence is observational, the aerosol formulation is hazardous to staff and the cost is high.
Supportive care	Oxygen, hydration	The actual treatment. Bronchodilators, corticosteroids and antibiotics have no role in uncomplicated bronchiolitis D-I.

17.2 Human metapneumovirus

Clinically indistinguishable from RSV, with no licensed antiviral and no vaccine C-III. Ribavirin and IVIG are occasionally used in HCT recipients on the basis of case series only C-III. Management is supportive.

17.3 Parainfluenza viruses 1--4

HPIV-1 is the classic cause of croup; HPIV-3 causes bronchiolitis and pneumonia and is a significant pathogen after HCT. **No antiviral has proven efficacy** C-III. DAS181, a recombinant sialidase fusion protein that removes the sialic acid receptor from respiratory epithelium, has shown promise in compassionate-use and trial settings C-II but is not licensed. Ribavirin is not recommended D-II. For croup, **corticosteroids** (dexamethasone) and nebulised adrenaline are the evidence-based treatments A-I — an important reminder that the correct therapy for a viral illness is often not an antiviral.

17.4 Measles

MOLECULAR VIROLOGY

A morbillivirus using **CD150 (SLAM)** on immune cells and **nectin-4** on epithelium. The profound and prolonged immunosuppression it causes — "immune amnesia", the depletion of pre-existing memory lymphocyte repertoires — explains the excess mortality from other infections for years afterwards, and is the strongest single argument for vaccination.

BEDSIDE — REGIMEN, DOSE, MONITORING

No licensed antiviral C-III. **Vitamin A** 50 000–200 000 IU by age, on two consecutive days, reduces mortality and should be given to every hospitalised child with measles A-I. Ribavirin has been used in severe disease and SSPE without convincing benefit C-III. Post-exposure: MMR within 72 hours, or immunoglobulin within 6 days for infants, pregnant women and the immunocompromised A-II.

17.5 Mumps and rubella

No antiviral therapy for either E-III; management is supportive and the interventions are vaccination and, for congenital rubella, prevention. Rubella in the first trimester carries a congenital rubella syndrome risk approaching 90%, which no treatment modifies.

17.6 Nipah and Hendra viruses

Henipaviruses with fruit-bat reservoirs, causing encephalitis with case fatality of 40–75%. **m102.4**, a human monoclonal antibody against the G glycoprotein, is available on a compassionate basis and has been used for post-exposure prophylaxis C-III. **Remdesivir** has efficacy in non-human primate models and is a reasonable therapeutic choice in an outbreak C-III. Ribavirin was used in the original Malaysian outbreak with equivocal results C-II. No licensed product exists; management is supportive with strict infection control.

18 Enteroviruses, rhinoviruses and parechoviruses

MOLECULAR VIROLOGY

Picornaviruses: small, non-enveloped, positive-sense RNA viruses translated from an IRES into a single polyprotein cleaved by the 2A and 3C proteases. Three drug targets have been pursued: the **VP1 hydrophobic pocket** (capsid binders such as pleconaril and vapendavir, which prevent uncoating), the **3C protease** (rupintrivir), and the **2C ATPase** (fluoxetine, repurposed). None is licensed.

CLINICAL VIROLOGY — ASSAY & INTERPRETATION

PCR on CSF, stool, throat and blood. **Parechovirus requires a specific PCR** — it is not detected by enterovirus assays, and is a cause of sepsis-like illness and encephalitis in young infants that is missed when only an enterovirus PCR is sent. Stool positivity can persist for weeks and does not prove current disease.

BEDSIDE — REGIMEN, DOSE, MONITORING

- **Enteroviral meningitis:** supportive; no antiviral E-III.
- **Neonatal enteroviral sepsis / myocarditis: IVIG** with high neutralising titre is used C-II; pleconaril showed a shortened time to culture negativity and a survival signal in a placebo-controlled trial but was never licensed C-I.
- **Chronic enteroviral meningoencephalitis in agammaglobulinaemia:** high-dose IVIG, including intraventricular administration in refractory cases C-III. Fluoxetine has been tried C-III.

- **Enterovirus D68 with acute flaccid myelitis:** no proven therapy; IVIG, corticosteroids and plasma exchange are used without good evidence C-III.
- **Enterovirus A71 hand-foot-and-mouth disease with brainstem encephalitis:** IVIG and milrinone are used in Asian practice C-II; an inactivated EV-A71 vaccine is licensed in China A-I.
- **Rhinovirus:** no antiviral, and the pharmacodynamic reason is instructive — viral replication peaks at or before symptom onset, so a drug given when the patient presents is already too late. A positive rhinovirus PCR should prompt antibacterial de-escalation A-III.
- **Poliovirus:** eradication-phase management. **Pocapavir** and **V-073**, capsid inhibitors, are available through compassionate-use protocols to clear prolonged poliovirus excretion in immunodeficient individuals (iVDPV) C-III — a genuine public-health indication, since these individuals are a reservoir threatening eradication.
- **Hepatitis A** is a picornavirus and is covered in §13.

19 Adenoviruses, polyomaviruses, papillomaviruses and parvovirus B19

19.1 Adenovirus

MOLECULAR VIROLOGY

Non-enveloped dsDNA viruses, over 100 types in seven species (A–G), encoding their own DNA polymerase, terminal protein and protease. Species C types establish persistent infection in mucosal lymphocytes and reactivate after transplantation; species B (types 11, 34, 35) are associated with haemorrhagic cystitis and nephritis.

CLINICAL VIROLOGY — ASSAY & INTERPRETATION

Quantitative plasma PCR. In paediatric allogeneic HCT, weekly surveillance with a defined threshold (commonly $\geq 10^3$–10^4 copies/mL, or any rising trend) triggers pre-emptive therapy B-II. Stool and respiratory positivity are common and do not alone warrant treatment.

BEDSIDE — REGIMEN, DOSE, MONITORING

- **Reduce immunosuppression** where possible — the single most effective intervention B-II.
- **Cidofovir** 5 mg/kg weekly, or 1 mg/kg three times weekly (the lower-dose regimen is better tolerated), with probenecid and hydration B-II. The evidence is observational throughout.
- **Brincidofovir** (lipid conjugate, oral, no nephrotoxicity, no OAT1 uptake) showed activity but its development for adenovirus was discontinued; it is now licensed for smallpox C-II.
- **Adenovirus-specific T cells** B-II where available — arguably the most effective intervention in refractory disseminated disease.
- **Epidemic keratoconjunctivitis and pharyngoconjunctival fever:** supportive; no antiviral E-III.

19.2 BK polyomavirus

MOLECULAR VIROLOGY

A small dsDNA virus replicating with **host** DNA polymerase, using large T antigen as its helicase. There is therefore **no virus-encoded polymerase to inhibit**, which is the fundamental reason no effective antiviral exists.

CLINICAL VIROLOGY — ASSAY & INTERPRETATION

Urinary BK DNA or decoy cells indicate replication, not disease: up to 30% of kidney transplant recipients have viruria. **Plasma DNAemia** is the actionable marker; sustained levels above roughly 10^4 copies/mL suggest probable nephropathy, and definitive diagnosis is by allograft biopsy with SV40 large T antigen immunostaining.

BEDSIDE — REGIMEN, DOSE, MONITORING

Reduction of immunosuppression is the treatment A-II — typically reducing the antimetabolite first, then the calcineurin inhibitor. Cidofovir, brincidofovir, leflunomide, IVIG, fluoroquinolones and everolimus have all been used; **none has convincing efficacy data** C-III, and fluoroquinolone prophylaxis has been shown ineffective in randomised trials D-I. BK-specific T cells are promising C-II. For haemorrhagic cystitis after HCT, management is supportive with hydration and bladder irrigation B-III.

19.3 JC polyomavirus

Causes **progressive multifocal leukoencephalopathy**, a demyelinating disease of oligodendrocytes, in HIV with advanced immunosuppression, on natalizumab and other immunomodulators, and in haematological malignancy. **There is no antiviral therapy** E-II: mefloquine, mirtazapine (a 5-HT_{2A} receptor antagonist, since JCV uses that receptor for entry), cytarabine and cidofovir have all failed. **The only effective treatment is restoration of immune function** — ART in HIV A-II, plasma exchange to remove natalizumab B-II, withdrawal of the offending immunosuppressant. Anticipate immune reconstitution inflammatory syndrome, which may require corticosteroids B-III. Pembrolizumab and JCV-specific T cells have shown benefit in small series C-III.

19.4 Human papillomavirus

MOLECULAR VIROLOGY

Non-enveloped dsDNA viruses replicating with host polymerase in differentiating squamous epithelium; **E6 and E7** degrade p53 and Rb respectively, driving the oncogenesis of cervical, anal, oropharyngeal, vulvar, vaginal and penile cancer.

BEDSIDE — REGIMEN, DOSE, MONITORING

There is no systemic antiviral E-III. Management is ablative or immunomodulatory: imiquimod (TLR7 agonist), podophyllotoxin, trichloroacetic acid, cryotherapy, excision. Cidofovir has been used topically or intralesionally for recurrent respiratory papillomatosis C-III, alongside bevacizumab B-III. **Prophylactic vaccination is the intervention that matters** — the nonavalent vaccine prevents the great majority of HPV-attributable cancer A-I, and population-level data now demonstrate near-elimination of cervical cancer in early-vaccinated cohorts.

19.5 Parvovirus B19

MOLECULAR VIROLOGY

The only human pathogenic ssDNA virus (class II), using the **P antigen (globoside)** receptor on erythroid progenitors — hence its tropism and its syndromes. Replication is entirely dependent on host polymerase in S-phase cells. **There is no antiviral target and no antiviral drug** E-III.

BEDSIDE — REGIMEN, DOSE, MONITORING

- **Erythema infectiosum, arthropathy:** supportive.
- **Transient aplastic crisis** in haemolytic anaemia: transfusion.
- **Pure red cell aplasia in the immunocompromised: IVIG** (e.g. 400 mg/kg/day for 5–10 days) is effective because commercial immunoglobulin contains high-titre neutralising antibody B-II; restore immune function where possible.
- **Hydrops fetalis:** intrauterine transfusion A-II.

19.6 Torque teno virus

An anellovirus, essentially universal and non-pathogenic, whose load tracks net immunosuppression. It is emerging as a **biomarker of immune competence** in transplant medicine C-II rather than a therapeutic target — included here because it increasingly appears on metagenomic reports and must not be treated.

20 Poxviruses

MOLECULAR VIROLOGY

Large, complex, brick-shaped dsDNA viruses that replicate **entirely in the cytoplasm** within discrete factories, carrying their own transcription apparatus in the virion because they never access the nucleus. They produce two infectious forms: the intracellular mature virion (IMV) and the extracellular enveloped virion (EEV), which mediates spread within the host. Two drugged steps:

- **E9L DNA polymerase** — inhibited by cidofovir and its lipid conjugate brincidofovir.
- **p37 (VP37, *F13L*)** — a palmitoylated protein required to wrap IMV in Golgi-derived membranes to form EEV. **Tecovirimat** blocks this step. The virus still replicates; what it cannot do is spread. This matters clinically: tecovirimat is not virucidal and depends on host immunity to clear the residual infection.

Orthopoxvirus egress and the tecovirimat block FIGURE 20.1

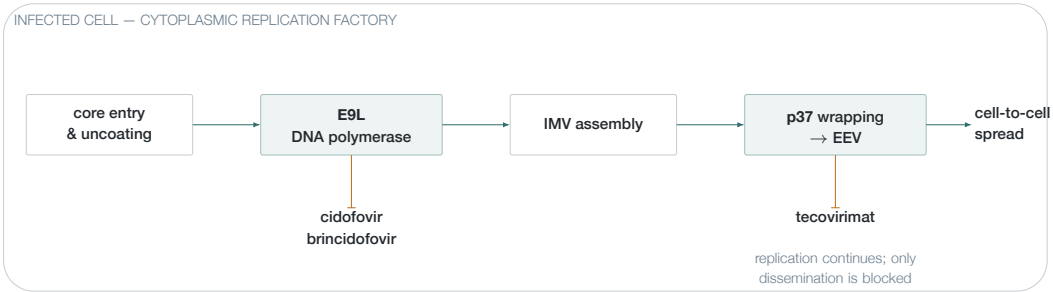


FIGURE 20.1. Tecovirimat is a dissemination inhibitor, not a replication inhibitor. Its clinical effect therefore depends on host immune clearance of virus already made — the likely explanation for its disappointing performance in trials conducted in people with advanced untreated HIV.

BEDSIDE — REGIMEN, DOSE, MONITORING

Mpox

- **Most cases are self-limiting** and need analgesia, wound care and management of proctitis A-III.
- **Tecovirimat** 600 mg bd (weight-banded) for 14 days has been the main antiviral used — but the randomised evidence is now discouraging: the PALM007 trial in the Democratic Republic of the Congo found **no reduction in time to lesion resolution**, although overall mortality was low with supportive care, and the STOMP trial in a predominantly clade II population likewise did not show benefit. Tecovirimat should therefore be regarded as **unproven** C-I and restricted to severe disease, ocular involvement and profoundly immunocompromised patients, ideally within a trial.
- **Advanced HIV with CD4 <200** is the dominant risk factor for severe, necrotising and fatal mpox. **ART is the critical intervention** A-II.
- **Brincidofovir** C-III and **cidofovir** C-III are alternatives; **vaccinia immune globulin** is used in severe disease and in those with contraindications to vaccination C-III.
- **Tecovirimat resistance** (*F13L* substitutions) emerges readily during monotherapy in immunocompromised patients with prolonged infection monotherapy selects resistance.
- **Vaccination** with MVA-BN is the effective population measure A-II.

Smallpox (variola)

Eradicated; retained only in two designated laboratories. In the event of release, **tecovirimat** B-III and **brincidofovir** B-III are licensed on the Animal Rule (efficacy inferred from animal models), with vaccinia immune globulin and vaccination. No human efficacy data exist, by definition.

Other poxviruses

Molluscum contagiosum: self-limiting; berdazimer gel and cantharidin are licensed topical options B-I, but observation is reasonable in immunocompetent children. Extensive molluscum in HIV responds to ART A-II. **Orf and pseudocowpox**: occupational, self-limiting, supportive E-III. **Vaccinia complications** (eczema vaccinatum, progressive vaccinia): vaccinia immune globulin plus tecovirimat C-III.

21 Rabies, arboviral flaviviruses and alphaviruses

21.1 Rabies

MOLECULAR VIROLOGY

A bullet-shaped rhabdovirus that travels retrogradely along axons to the CNS, largely shielded from humoral immunity throughout. This anatomical privilege is why post-exposure prophylaxis works and why treatment of established disease does not.

BEDSIDE — REGIMEN, DOSE, MONITORING

Post-exposure prophylaxis is an emergency and is close to 100% effective when done correctly A-I:

1. **Immediate, thorough wound washing** with soap and water for 15 minutes — the single most effective step, and the one most often omitted.
2. **Rabies immunoglobulin** (human RIG 20 IU/kg or equine 40 IU/kg) infiltrated *into and around the wound*, for category III exposures in previously unvaccinated patients. Infiltration matters more than the systemic dose.
3. **Vaccine** on a recognised schedule (Essen, Zagreb, or intradermal regimens). Previously vaccinated patients need vaccine only, no RIG.

There is no effective treatment for established rabies E-II. The Milwaukee protocol has not been reproducibly successful and is not recommended D-II; management of clinical rabies is palliative.

21.2 Dengue

MOLECULAR VIROLOGY

Four antigenically distinct serotypes. **Antibody-dependent enhancement** — cross-reactive but non-neutralising antibody from a prior serotype facilitating FcγR-mediated uptake — is why second infections are more severe, and why vaccines must be used with care.

BEDSIDE — REGIMEN, DOSE, MONITORING

No antiviral is licensed E-I: chloroquine, balapiravir, celgosivir, prednisolone and ivermectin have all failed in trials. **Fluid management is the treatment**, guided by the WHO warning-sign framework, with crystalloid during the critical plasma-leak phase A-I. **Avoid NSAIDs and aspirin** D-II. Vaccines: Dengvaxia requires documented prior infection A-I; TAK-003 is licensed in several countries without a pre-vaccination screening requirement A-I.

21.3 Zika, West Nile, Japanese encephalitis, tick-borne encephalitis, yellow fever

- **Zika:** no antiviral E-III; the clinical issues are congenital Zika syndrome and Guillain–Barré syndrome, managed supportively, with preconception counselling and vector avoidance.
- **West Nile:** no antiviral E-II; ribavirin and interferon have failed. Supportive care; IVIG with high anti-WNV titre has been studied without definitive benefit C-II.
- **Japanese encephalitis:** no antiviral E-I — ribavirin, interferon alfa and dexamethasone were all negative in randomised trials. An effective vaccine exists A-I.
- **Tick-borne encephalitis:** no antiviral; effective vaccine A-I.
- **Yellow fever:** no antiviral E-III; supportive care, and a highly effective single-dose live vaccine conferring lifelong immunity A-I.

21.4 Chikungunya and other alphaviruses

Chikungunya causes an acute febrile arthralgia that becomes chronic in up to a third. **No antiviral** E-III; NSAIDs and, for chronic arthritis, methotrexate or hydroxychloroquine C-II. Live-attenuated and virus-like-particle vaccines are now licensed A-I. Ross River, Mayaro, O'nyong-nyong and Sindbis viruses are managed identically. **Eastern equine encephalitis** carries high mortality and has no specific therapy E-III.

22 Viral haemorrhagic fevers: filoviruses, arenaviruses, bunyavirales

This is the one group in which the therapeutic landscape has genuinely transformed in a decade — but only for Ebola virus (*Zaire ebolavirus*) specifically, and the transformation does not transfer to its relatives.

22.1 Ebola and Marburg

MOLECULAR VIROLOGY

Filamentous negative-sense RNA viruses. The surface glycoprotein GP mediates entry via macropinocytosis and endosomal **Niemann–Pick C1 (NPC1)** after cathepsin cleavage. The licensed therapeutics are monoclonal antibodies against GP; remdesivir targets the L polymerase.

BEDSIDE — REGIMEN, DOSE, MONITORING

Agent	Target	Position
Ansuvimab (mAb114)	*Zaire ebolavirus* GP	A-I. Single infusion. Superior to ZMapp in the PALM randomised trial.
Atoltivimab/maftivimab/odesivimab (REGN-EB3)	*Zaire ebolavirus* GP	A-I. Also superior to ZMapp in PALM.
Remdesivir	L polymerase	Inferior to both mAbs in PALM C-I; reserve for species not covered by the antibodies.
Ervebo (rVSV-ZEBOV) vaccine	—	A-I for outbreak ring vaccination and for at-risk health workers.

The critical caveat: both licensed monoclonals are specific to *Zaire ebolavirus*. They are **not** expected to work against *Sudan ebolavirus* or against **Marburg virus** E-II, for which there is no licensed therapy or vaccine and for which management remains aggressive supportive care with investigational agents under outbreak protocols. Ervebo likewise does not protect against Sudan virus.

22.2 Lassa fever

An Old World arenavirus with a *Mastomys* rodent reservoir; endemic in West Africa, with sensorineural hearing loss in a quarter of survivors and high fetal loss. **Ribavirin** has been standard of care since a 1986 observational study, but that study has been substantially re-analysed and criticised for immortal time bias and design flaws, and more recent data suggest **possible harm** in some groups. Its use should now be regarded as **uncertain** C-II rather than established. Supportive care, aggressive fluid and electrolyte management, and dialysis where available drive outcome. Favipiravir and monoclonal cocktails are in development.

22.3 Crimean--Congo haemorrhagic fever

A nairovirus transmitted by *Hyalomma* ticks and by nosocomial blood contact, with mortality of 10–40%. **Ribavirin** is widely used but randomised and meta-analytic evidence does not demonstrate benefit C-II. Supportive care with blood product support is the mainstay. Strict infection control is essential — CCHF is a notable cause of healthcare-worker infection.

22.4 Hantaviruses

- **Haemorrhagic fever with renal syndrome** (Hantaan, Puumala, Seoul, Dobrava): supportive, with renal replacement therapy. IV ribavirin showed benefit in an early Chinese trial C-II; it is not standard practice.
- **Hantavirus cardiopulmonary syndrome** (Sin Nombre, Andes): **no antiviral** E-II — ribavirin has been negative in trials. Early transfer to a centre capable of **veno-arterial ECMO** is the intervention that changes survival B-II. Andes virus is notable for person-to-person transmission.

22.5 Rift Valley fever, Oropouche and other bunyavirales

No licensed antivirals E-III; supportive care and vector control. Oropouche virus has expanded substantially in the Americas with reports of vertical transmission; management is supportive.

22.6 Severe fever with thrombocytopenia syndrome

A bandavirus transmitted by *Haemaphysalis* ticks in East Asia, with mortality of 6–30%. Favipiravir has shown a mortality signal in observational studies and in a Japanese trial in patients with lower viral loads C-II; plasma exchange is used C-III. Nosocomial and contact transmission occurs.

22.7 Lymphocytic choriomeningitis virus

An arenavirus with a house-mouse reservoir, causing aseptic meningitis and, in pregnancy, congenital hydrocephalus and chorioretinitis. It is also a recognised cause of fatal transplant-transmitted infection. Ribavirin has *in vitro* activity and has been used C-III; management is otherwise supportive.

23 Viral gastroenteritis

No antiviral is licensed for any cause of viral gastroenteritis. The content of this section is therefore mostly about what not to do, and about the one population in which the absence of therapy is a genuine clinical problem.

23.1 Norovirus

A calicivirus and the commonest cause of epidemic gastroenteritis worldwide, with an exceptionally low infectious dose and prolonged environmental survival. **Histo-blood group antigen** expression determines susceptibility — *FUT2* non-secretors are resistant to the dominant GII.4 genotypes.

Treatment is rehydration A-I. **Nitazoxanide** has been studied with inconsistent results C-II. In chronic norovirus of the immunocompromised — which can cause months of diarrhoea, malnutrition and graft dysfunction — reduction of immunosuppression, oral immunoglobulin, nitazoxanide and ribavirin have all been tried without consistent benefit C-III. **Alcohol hand rub is unreliable against norovirus**; soap-and-water handwashing and chlorine-based environmental decontamination are required A-II.

23.2 Rotavirus

A segmented dsRNA reovirus; the former leading cause of childhood diarrhoeal death. **Oral rehydration solution and zinc** are the treatment A-I; **nitazoxanide** shortens illness modestly C-II. **Live oral vaccines** (Rotarix, RotaTeq and others) have been transformative A-I, with a small intussusception risk that is far outweighed by benefit. In severe combined immunodeficiency, vaccine-strain rotavirus can cause prolonged infection — an argument for newborn screening before vaccination.

23.3 Sapovirus, astrovirus, enteric adenovirus (types 40/41)

Supportive care only E-III. Astrovirus has been reported as a cause of encephalitis in immunocompromised patients, identified by metagenomic sequencing, with no established therapy C-III.

PART III

Cross-cutting practice

24 Drug interactions

Antivirals generate more clinically significant interactions than any other class in the hospital formulary, and almost all of it comes from a small number of mechanisms. Learn the mechanisms and the individual pairs become predictable.

24.1 The five mechanisms that account for most antiviral interactions

1. Potent CYP3A4 inhibition — ritonavir and cobicistat. Both are used deliberately as pharmacokinetic boosters. They raise the concentration of *every* CYP3A4 substrate, often severalfold. The classic preventable harms are: iatrogenic Cushing syndrome and adrenal suppression with **inhaled or injected corticosteroids** (fluticasone, budesonide, triamcinolone — use beclometasone or prednisolone instead); rhabdomyolysis with simvastatin or lovastatin **(contraindicated)**; excessive sedation with midazolam; calcineurin inhibitor toxicity; bleeding with rivaroxaban or apixaban; and ergotism. Cobicistat additionally inhibits tubular creatinine secretion, producing a benign rise in serum creatinine of 10–15 μmol/L that is *not* a fall in true GFR.

2. Enzyme induction — rifamycins, efavirenz, carbamazepine, phenytoin, St John's wort. **Rifampicin is contraindicated with almost every boosted regimen, with all INSTIs at standard dose, with rilpivirine and with doravirine.** Where rifamycin therapy is unavoidable, rifabutin is the preferred agent and dolutegravir is dosed twice daily. Induction persists for 1–2 weeks after the inducer stops.

3. Transporter inhibition — letermovir. Letermovir is a moderate CYP3A inhibitor *and* an inhibitor of OATP1B1/3. It raises **tacrolimus, ciclosporin, sirolimus** and statin concentrations substantially. Reduce letermovir to 240 mg daily when given with ciclosporin, and monitor calcineurin inhibitor levels closely when letermovir is started *and* when it is stopped — the rebound fall in tacrolimus on stopping causes rejection.

4. Chelation and pH-dependent absorption. Polyvalent cations (calcium, magnesium, aluminium, iron, zinc) chelate **dolutegravir, bictegravir, raltegravir and baloxavir**; separate dosing or take with food. Acid suppression impairs absorption of **atazanavir, rilpivirine, ledipasvir and velpatasvir**; proton pump inhibitors are contraindicated with rilpivirine.

5. Additive organ toxicity. Tenofovir disoproxil with other nephrotoxins; ganciclovir or valganciclovir with mycophenolate, cotrimoxazole, linezolid or azathioprine (additive myelosuppression); foscarnet with amphotericin or aminoglycosides; cidofovir with any nephrotoxin **(NSAIDs and aminoglycosides must be stopped)**.

24.2 Pairs worth committing to memory

Combination	Effect	Action
Ritonavir/cobicistat + inhaled fluticasone	Cushing syndrome, adrenal suppression	Switch to beclometasone; this is common and entirely preventable.
Ritonavir/cobicistat + simvastatin or lovastatin	Rhabdomyolysis	**Contraindicated.** Use pravastatin or low-dose atorvastatin/rosuvastatin.
Nirmatrelvir/ritonavir + tacrolimus	Profound tacrolimus toxicity	Specialist input; hold or markedly reduce the calcineurin inhibitor with level monitoring, or use remdesivir instead.
Rifampicin + any boosted PI or INSTI	Loss of virological control	Use rifabutin; double dolutegravir; avoid boosted regimens.
Letermovir + tacrolimus/ciclosporin	Raised levels, then rebound fall on stopping	Monitor at start **and** at stop.
Sofosbuvir + amiodarone	Symptomatic bradycardia, cardiac arrest	**Contraindicated** E-II.
Valganciclovir + mycophenolate	Additive neutropenia	Monitor FBC twice weekly; G-CSF.
Cidofovir + NSAIDs/aminoglycosides	Severe nephrotoxicity	Stop the co-administered nephrotoxin; probenecid and hydration are mandatory.
Dolutegravir + metformin	Raised metformin (OCT2 inhibition)	Cap metformin at 1 g daily.
Dolutegravir + calcium/iron	Loss of efficacy	Separate by 2 h or take with food.
Baloxavir + dairy or antacids	Reduced absorption	Separate dosing.
Ribavirin + didanosine	Fatal lactic acidosis	**Contraindicated**.
Ribavirin + azathioprine	Myelotoxicity via IMPDH inhibition	Avoid.
Tenofovir disoproxil + NSAIDs	Acute kidney injury, Fanconi	Prefer TAF; avoid NSAIDs.

PRACTICAL RULE

Before starting any boosted antiviral, any letermovir, or any rifamycin in a patient on antivirals, run the *whole* medication list — including inhalers, eye drops, over-the-counter products, herbal preparations and recreational drugs — through a dedicated interaction resource. The University of Liverpool interaction databases for HIV, hepatitis and COVID-19 are the reference standard and are free.

25 Toxicity and monitoring

Agent	Principal toxicity	Monitoring and mitigation
Aciclovir / valaciclovir	Crystal nephropathy; neurotoxicity (tremor, myoclonus, agitation, hallucinations); phlebitis	Dose on ideal body weight; hydrate; infuse over ≥1 h; adjust for CrCl. Neurotoxicity is commonly misread as worsening encephalitis — the distinguishing features are myoclonus and a temporal relationship to dosing. Haemodialysis clears the neurotoxic metabolite.
Ganciclovir / valganciclovir	Neutropenia, thrombocytopenia, anaemia; carcinogenic and teratogenic in animals; infertility	FBC at least twice weekly during induction. Use G-CSF rather than dose reduction when virus is still replicating. Counsel about fertility.
Foscarnet	Nephrotoxicity; calcium, magnesium, potassium and phosphate wasting; seizures from acute ionised hypocalcaemia; penile/vulval ulceration	Pre- and post-hydration with saline; daily electrolytes including **ionised** calcium and magnesium during induction; recalculate the dose for every change in CrCl; aggressive replacement.
Cidofovir	Dose-limiting, partly irreversible proximal tubular nephrotoxicity; Fanconi syndrome; neutropenia; **ocular hypotony and uveitis**	Mandatory probenecid and 1 L saline pre-hydration; check creatinine and urine protein before every dose; stop all other nephrotoxins; ophthalmology review.
Tenofovir disoproxil	Proximal tubulopathy, Fanconi syndrome, reduced bone mineral density	Creatinine, phosphate, urine protein:creatinine and glucose. Switch to TAF if concerned.
Tenofovir alafenamide	Weight gain, dyslipidaemia	Lipids and weight.
Abacavir	**Hypersensitivity reaction** (fever, rash, GI and respiratory symptoms; rechallenge can be fatal)	**HLA-B*57:01 testing is mandatory before use** A-I. Never rechallenge.
NRTIs (older: d4T, ddI, AZT)	Mitochondrial toxicity via pol γ: lactic acidosis, lipoatrophy, peripheral neuropathy, pancreatitis; AZT causes anaemia	Largely obsolete; this is why.
Efavirenz	CNS effects, vivid dreams, depression, suicidality; QT	*CYP2B6* slow metabolisers reach very high concentrations; TDM if symptomatic.
Dolutegravir, bictegravir	Weight gain; insomnia; small creatinine rise from OCT2 inhibition (not true GFR change)	Weight and metabolic monitoring.
Protease inhibitors	Dyslipidaemia, insulin resistance, GI intolerance; atazanavir causes unconjugated hyperbilirubinaemia (benign)	Lipids, glucose.
Ribavirin	**Haemolytic anaemia** (dose-limiting); teratogenicity	FBC weekly initially; contraception during and for 6 months after, in both sexes E-II.
Maribavir	Dysgeusia (metallic taste) in ~50%; nausea; raised tacrolimus	Counsel in advance — it drives discontinuation; monitor tacrolimus.
Letermovir	Generally very well tolerated; interactions are the issue	Calcineurin levels.
Remdesivir	Transaminitis; infusion reactions; bradycardia	LFTs.
Nirmatrelvir/ritonavir	Dysgeusia; the interaction burden	Full medication review.
Molnupiravir	Mutagenic mechanism; contraindicated in pregnancy	Contraception advice.
Oseltamivir	Nausea and vomiting; neuropsychiatric events reported, causality unclear	Take with food.
Interferon alfa	Influenza-like illness, cytopenias, depression, thyroid and autoimmune disease, retinopathy	TSH, FBC, mood assessment; avoid in autoimmune disease and decompensated cirrhosis.
Bulevirtide	Asymptomatic bile-salt elevation; injection-site reactions	Expected; not a reason to stop.
Tecovirimat	Generally well tolerated; headache, nausea	—
Brincidofovir	Diarrhoea, transaminitis	LFTs.

26 The immunocompromised host: strategy rather than drug choice

In the immunocompromised patient the dominant determinant of outcome is almost never which antiviral is chosen. It is whether immune function can be restored, whether the strategy is prophylactic or pre-emptive, and whether the diagnosis is disease or detection.

26.1 Three strategies, and when each is correct

Strategy	Definition	When it is preferred
Universal prophylaxis	Antiviral given to all at-risk patients for a defined period	Highest-risk groups where breakthrough is costly: CMV D+/R− solid organ transplant, lung and intestinal transplant, letermovir in seropositive allogeneic HCT. Advantages: prevents indirect immunomodulatory effects, simple. Disadvantages: drug toxicity in patients who would never have reactivated, cost, and **late-onset disease** after prophylaxis stops.
Pre-emptive therapy	Scheduled surveillance testing; treat when a threshold is crossed, before symptoms	CMV R+ solid organ transplant, adenovirus and EBV after HCT. Advantages: less drug exposure, less toxicity. Disadvantages: requires reliable weekly testing and rapid turnaround; misses compartmental disease that does not produce DNAemia.
Therapy of established disease	Treat the syndrome	Always, and in addition to the above when they fail.

26.2 Restoring immunity is the intervention

- **HIV:** start ART. Progressive multifocal leukoencephalopathy, Kaposi sarcoma, cryptosporidiosis, molluscum, severe mpox and chronic enteroviral infection all respond to immune reconstitution and to nothing else A-II. Anticipate and manage IRIS.
- **Transplantation:** reduce immunosuppression. This is first-line therapy for BK nephropathy A-II, PTLD A-II, chronic HEV A-II, adenovirus B-II and JC-PML B-II.
- **B-cell depletion:** consider immunoglobulin replacement in secondary hypogammaglobulinaemia with recurrent infection B-II.
- **Virus-specific T cells.** Donor-derived or third-party banked VSTs against CMV, EBV, adenovirus, BKV and HHV-6 produce durable responses in refractory post-transplant viral disease B-II, and represent the most important therapeutic advance in this field that is not a small molecule.

26.3 Prolonged replication is where resistance is made

Every resistant virus described in this book — aciclovir-resistant HSV, *UL97*-mutant CMV, `I38T` influenza, tecovirimat-resistant mpox, intrahost SARS-CoV-2 evolution — arises overwhelmingly in patients with impaired immunity, prolonged replication and continuous drug exposure. Three practical consequences follow:

1. **Do not dose-reduce in the face of ongoing replication.** Support the toxicity instead (G-CSF, transfusion, electrolyte replacement).
2. **Avoid monotherapy with low-barrier agents** in this population — baloxavir, letermovir for treatment, tecovirimat for prolonged mpox.
3. **Treat to clearance, not to a fixed duration,** and confirm clearance before stopping.

27 Where the field is going

Functional cure of hepatitis B. The target is cccDNA silencing or elimination plus HBsAg loss. Approaches in development: **siRNA and antisense oligonucleotides** (bepirovirsen, xalnesiran) to suppress all viral transcripts including HBsAg; **capsid assembly modulators**; **entry inhibition**; therapeutic vaccination; and checkpoint modulation to restore exhausted HBV-specific T cells. Combination will almost certainly be required.

HIV without daily tablets. Long-acting injectable cabotegravir/rilpivirine is established; lenacapavir has moved six-monthly dosing from aspiration to practice, both for treatment and for pre-exposure prophylaxis, where its efficacy has been exceptional. Broadly neutralising antibodies, capsid inhibitors with still longer half-lives, and "shock and kill" or "block and lock" reservoir strategies remain in trials.

Oral antivirals for respiratory pandemics. Obeldesivir (an oral nucleoside prodrug related to remdesivir), next-generation M^{pro} inhibitors without a ritonavir booster, and host-directed agents. The lesson repeatedly learned is that treatment must start within the first days and must therefore be oral, cheap and widely distributed.

Helicase--primase inhibition for herpes simplex. Pritelivir and amenamevir act independently of thymidine kinase, retain activity against aciclovir-resistant virus, and may reduce shedding more effectively than nucleoside analogues.

Antivirals for the undrugged. Rhinovirus, norovirus, BK, JC, parvovirus B19, measles and the arboviruses remain without therapy. The barriers differ — pharmacodynamic timing for rhinovirus, host-polymerase dependence for the polyomaviruses and parvovirus, market failure for the arboviruses — and each requires a different solution.

Deep mutational scanning and structure-based resistance prediction. Systematically measuring the fitness and susceptibility consequences of every possible substitution in a target, before a drug is deployed, would let resistance be anticipated rather than discovered. This is now technically feasible and is the most likely near-term change to how the field handles resistance.

Pan-family antivirals. Targeting conserved enzymatic folds — coronavirus M^{pro} across the family, flavivirus NS5, picornavirus 3C — to have therapy ready before the next emergence rather than after it.

PART IV

Appendices

A Antiviral spectrum matrix

Read down a column to answer “what can I use against this virus?” and across a row to answer “what does this drug cover?” **A** = established, licensed or guideline-supported; **b** = used, weaker evidence; **–** = no useful activity or no role. This matrix is a prompt, not a prescription: every entry is qualified in the relevant chapter.

Agent	HSV	VZV	CMV	EBV	HHV6	HBV	HCV	HIV	Flu	CoV2	Adeno
Aciclovir / valaciclovir	A	A	–	b	–	–	–	–	–	–	–
Penciclovir / famciclovir	A	A	–	–	–	–	–	–	–	–	–
Ganciclovir / valganciclovir	b	b	A	b	b	–	–	–	–	–	–
Foscarnet	A	A	A	b	A	–	–	b	–	–	–
Cidofovir	b	b	b	–	b	–	–	–	–	–	b
Brincidofovir	b	b	b	–	b	–	–	–	–	–	b
Letermovir	–	–	A	–	–	–	–	–	–	–	–
Maribavir	–	–	A	–	–	–	–	–	–	–	–
Pritelivir / amenamevir	A	b	–	–	–	–	–	–	–	–	–
Tenofovir (TDF/TAF)	–	–	–	–	–	A	–	A	–	–	–
Entecavir	–	–	–	–	–	A	–	–	–	–	–
Bulevirtide	–	–	–	–	–	A†	–	–	–	–	–
Sofosbuvir-based DAAs	–	–	–	–	–	–	A	–	–	–	–
INSTIs, NNRTIs, PIs	–	–	–	–	–	–	–	A	–	–	–
Lenacapavir	–	–	–	–	–	–	–	A	–	–	–
Oseltamivir, zanamivir, peramivir	–	–	–	–	–	–	–	–	A	–	–
Baloxavir	–	–	–	–	–	–	–	–	A	–	–
Nirmatrelvir/r, ensitrelvir	–	–	–	–	–	–	–	–	–	A	–
Remdesivir	–	–	–	–	–	–	b	–	–	A	–
Molnupiravir	–	–	–	–	–	–	–	–	–	b	–
Ribavirin	–	–	–	–	–	–	b	–	–	–	–
Interferon alfa	–	–	–	–	–	A	b	–	–	–	–
Immunoglobulin / mAbs	b	A	b	–	–	A	–	b	–	b	–
Virus-specific T cells	–	–	b	b	b	b	–	–	–	–	b

† Bulevirtide is licensed for hepatitis D, not for hepatitis B monoinfection.

B Viruses for which there is no effective antiviral

This list is as clinically important as the formulary. Knowing that no agent works prevents toxic, expensive and futile treatment, and redirects effort to the interventions that do change outcome — supportive care, immune reconstitution, vaccination and infection control.

Virus	What actually changes outcome
Rhinovirus, seasonal coronaviruses	Nothing antiviral; stop antibacterials.
Norovirus, sapovirus, astrovirus	Rehydration; environmental decontamination with chlorine; soap-and-water handwashing.
Rotavirus	Oral rehydration, zinc; vaccination.
Measles	Vitamin A; vaccination; immunoglobulin post-exposure.
Mumps, rubella	Vaccination.
Parvovirus B19	IVIG in pure red cell aplasia; transfusion; intrauterine transfusion.
BK and JC polyomaviruses	Reduction of immunosuppression; ART; plasma exchange for natalizumab-associated PML.
Human papillomavirus	Ablation; vaccination.
Dengue, Zika, yellow fever, West Nile, Japanese encephalitis, tick-borne encephalitis	Fluid management (dengue); vaccination where available; vector control.
Chikungunya and other alphaviruses	Analgesia; vaccination.
Rabies (established disease)	Nothing. Pre- and post-exposure prophylaxis is close to completely effective and is the entire therapeutic opportunity.
Hantavirus cardiopulmonary syndrome	Early ECMO.
Crimean–Congo haemorrhagic fever	Supportive care and blood products; infection control.
Marburg and *Sudan ebolavirus*	Supportive care; the licensed monoclonals do not cover these.
Parainfluenza, human metapneumovirus	Supportive; corticosteroids for croup.
Enteroviruses (most syndromes), parechovirus	Supportive; IVIG in specific settings.
HTLV-1/2	No antiviral; zidovudine/interferon in selected ATL subtypes; prevention by donor screening and avoidance of breastfeeding.
Hepatitis A	Supportive; vaccination; post-exposure prophylaxis.
Torque teno virus and other anelloviruses	Nothing — they are not pathogens. Do not treat.
Chromosomally integrated HHV-6	Nothing. Recognise it and stop.

c Resistance quick reference

Virus	Gene	Key substitutions	What it means
HSV / VZV	*UL23*/*ORF36* (TK)	frameshifts in G-strings at codons 146, 430; nonsense; R176Q	~95% of resistance. Aciclovir, penciclovir lost; foscarnet and cidofovir retained.
HSV / VZV	*UL30*/*ORF28* (pol)	various	May confer cross-resistance to foscarnet and cidofovir.
CMV	*UL97*	M460V/I, H520Q, C592G, A594V, L595S, C603W	Ganciclovir only. Foscarnet, cidofovir, letermovir, maribavir retained. C480F additionally confers maribavir resistance.
CMV	*UL54*	F412C, D413E, V715M, A809V, V781I	Determines cross-resistance across ganciclovir, cidofovir and foscarnet.
CMV	*UL56*	C325Y/W/F	Letermovir, >3000-fold, single step.
CMV	*UL27*	T409M, H411Y	Maribavir (also arise in *UL97*).
HBV	*RT*	rtM204V/I ± rtL180M; rtA181T/V, rtN236T; rtT184, rtS202, rtM250	Lamivudine; adefovir; entecavir (requires rtM204V *plus* one more). Tenofovir retains activity.
HCV	*NS5A*	Y93H, L31M/V, Q30R	Relevant mainly to retreatment.
HCV	*NS5B*	S282T	Sofosbuvir; severe fitness cost, rarely persists.
HIV	*RT*	M184V, K65R, TAMs, K103N, Y181C, E138K	See §14.
HIV	*IN*	Q148H/R/K+G140S, N155H, Y143R, R263K	First- versus second-generation INSTI pathways.
Influenza	*NA*	H275Y (N1), R292K, E119V (N2)	Oseltamivir/peramivir; zanamivir usually retained with H275Y.
Influenza	*PA*	I38T/M/F	Baloxavir; treatment-emergent, especially in children.
Influenza A	*M2*	S31N	Adamantanes; fixed in circulating strains.
SARS-CoV-2	*nsp5*	E166V, L50F+E166V	Nirmatrelvir; uncommon.
SARS-CoV-2	*nsp12*	V792I, E802D	Remdesivir; described in prolonged immunocompromised infection.
Mpox	*F13L*	various	Tecovirimat; emerges on monotherapy in immunocompromised hosts.

D Abbreviations

ART	antiretroviral therapy
ATL	adult T-cell leukaemia/lymphoma
BAL	bronchoalveolar lavage
CpAM	core protein allosteric modulator
DNAemia	detectable viral DNA in blood
ExoN	3′ →5′ exoribonuclease (nsp14)
IMV	intracellular mature virion
IQ	inhibitory quotient
IU	international unit
NA	neuraminidase
NNRTI	non-nucleoside reverse transcriptase inhibitor
NTCP	sodium taurocholate cotransporting polypeptide
PML	progressive multifocal leukoencephalopathy
PrEP	pre-exposure prophylaxis
RAS	resistance-associated substitution
SVR12	sustained virological response at 12 weeks
TAM	thymidine-analogue mutation
TDM	therapeutic drug monitoring
VST	virus-specific T cells
cccDNA	covalently closed circular DNA
CrCl	creatinine clearance (Cockcroft–Gault)
CRRT	continuous renal replacement therapy
DAA	direct-acting antiviral
EEV	extracellular enveloped virion
HCT	haematopoietic cell transplantation
INSTI	integrase strand-transfer inhibitor
IRIS	immune reconstitution inflammatory syndrome
MUNANA	fluorogenic neuraminidase substrate
NGS	next-generation sequencing
NRTI	nucleos(t)ide reverse transcriptase inhibitor
PEP	post-exposure prophylaxis
PRA	plaque reduction assay
PTLD	post-transplant lymphoproliferative disorder
RdRp	RNA-dependent RNA polymerase
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TK	thymidine kinase
VZIG	varicella zoster immune globulin