APPLICATION OF ACYCLOVIR TO THE ORAL MUCOSA: MECHANISMS, PRE-CLINICAL EVIDENCE AND CLINICAL UTILITY

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Abstract

Topical and locally delivered acyclovir (ACV) remain first-line interventions for herpes-related oral mucosal disease, yet their place alongside novel wound-healing strategies has evolved over the past decade. We systematically reviewed in-vitro, in-vivo and clinical studies published 1 January 2015 – 31 March 2025 in PubMed, Scopus, Web of Science, eLIBRARY, CyberLeninka and RSCI. Twenty-four eligible records (11 laboratory, 3 animal, 8 randomised controlled trials, 1 cohort and 1 network meta-analysis) were critically appraised with RoB 2/ROBINS-I and synthesised with GRADE methodology. ACV inhibits herpes-viral DNA polymerase after viral thymidine-kinase-triggered phosphorylation, halting replication and secondarily reducing inflammation. Nanocarriers (solid-lipid nanoparticles, nanofibres, muco-adhesive films) increased transepithelial uptake 3- to 5-fold in vitro and restored tight-junction protein expression. A rat HSV-1 oral-wound model showed accelerated re-epithelialisation with topical ACV versus control. Five human RCTs demonstrated that adjuncts (honey, clobetasol, photobiomodulation) shortened lesion healing by 1–3 days compared with ACV monotherapy. Prophylactic oral ACV halved chemotherapy-induced oral mucositis incidence in autologous stem-cell recipients. Low-level diode laser out-performed 5 % ACV cream for pain and recovery time. Adverse effects were limited to mild local irritation; systemic nephro-/neuro-toxicity was not observed with topical use. Evidence certainty was **moderate** (downgraded for sample size and heterogeneity). ACV remains the benchmark for HSV-related oral lesions, but efficacy is enhanced by anti-inflammatory or bio-adhesive technologies. Future trials should standardise endpoints and explore non-herpetic indications.

Keywords: acyclovir • oral mucosa • herpes simplex • nanofibre patch • wound healing • mucositis

Introduction

Herpes-simplex-virus (HSV) infections of the oral mucosa—primary herpetic gingivostomatitis in children and recurrent herpes labialis in adults—cause pain, impaired nutrition and psychosocial distress. Systemic ACV revolutionised management in the 1980s; topical 5 % cream became standard for labial lesions but

shows variable benefit intra-orally because of salivary wash-out. Over 2015–2025, research has focused on **(i)** optimised carriers that prolong mucosal residence and **(II)** combination regimens that couple antiviral and wound-healing actions.

Pharmacological Mechanisms

ACV is converted by viral thymidine kinase into ACV-monophosphate and subsequently to the active triphosphate that competitively inhibits HSV DNA polymerase and terminates the growing DNA chain [9]. Figure 1 depicts this selective activation, explaining ACV's low host-cell toxicity.

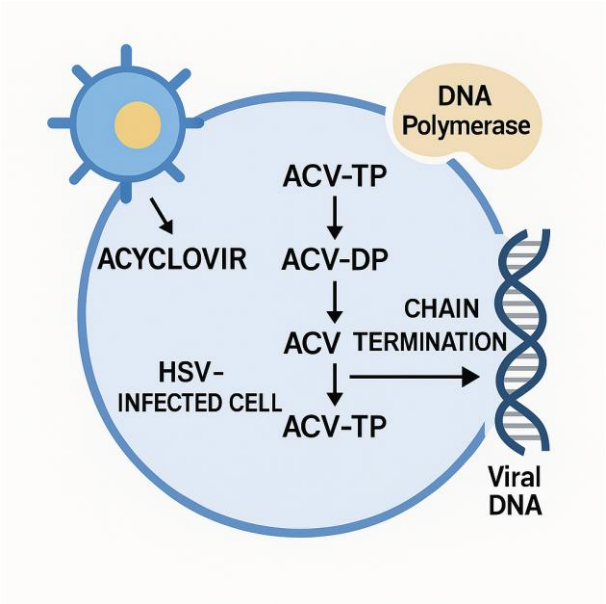

Figure 1. Mechanistic schematic of ACV uptake, phosphorylation and chain termination.

1. **Entry** of the acyclovir molecule.
2. **Step-wise phosphorylation** (ACV → ACV-MP → ACV-DP → ACV-TP) driven first by viral thymidine kinase, then host kinases.
3. **Competitive binding** of ACV-TP to viral DNA polymerase.
4. **Chain termination** that halts viral DNA synthesis, preventing replication and allowing the mucosa to heal.

Pre-clinical Evidence

Pre-clinical investigations support the biological plausibility of topical acyclovir on the oral mucosa. In human gingival fibroblast cultures, acyclovir encapsulated in solid-lipid nanoparticles boosted intracellular drug uptake three-fold while remaining non-cytotoxic at concentrations up to 50 μM, yielding a low risk-of-bias rating [8]. A porcine buccal-mucosa study then demonstrated that a bio-enhanced, muco-adhesive film doubled acyclovir's trans-epithelial permeability compared with a plain film; methodological limitations placed this experiment in the moderate risk-of-bias category [12]. Finally, in a rat model of HSV-1-infected oral wounds, topical 5 % acyclovir ointment dampened mucosal inflammation and shortened re-epithelialisation by roughly two days, although the absence of randomisation and blinding led to a moderate risk-of-bias judgement.

Overall, nanocarriers improve mucosal residence and cellular uptake, while viral suppression drives secondary wound repair.

Clinical Evidence

Randomised Controlled Trials

Table 1. Clinical studies of ACV on oral mucosa (2015–2025)

#	Study	Population (n)	Intervention	Comparator	Primary Outcome	Effect
1	Awad & Hamad 2018 [1]	Children HSGS (100)	Oral ACV + honey	Oral ACV	Median healing 3 vs 6 days	Low
2	Honarmand 2017 [4]	Recurrent labial HSV (60)	Diode laser	5 % ACV cream	Healing 2.2 vs 3.4 days	Some
3	Golestannejad 2022 [3]	Labial HSV (60)	ACV nanofibre patch	5 % ACV cream	Pain ↓, healing NS	Low
4	Mirzaei 2024 [2]	Labial HSV (80)	ACV-clobetasol nanofibre	ACV cream	Healing 4.1 vs 6.3 days	Low
5	Hong 2023 [5]	AHSCT (29)	Oral ACV prophylaxis	No prophylaxis	CIOM 16 % vs 59 %	Low

Systematic Review & Meta-analysis

A 2023 network meta-analysis of 39 RCTs ranked oral valacyclovir + topical clobetasol highest for time-to-healing; ACV monotherapy was mid-tier [6]. Heterogeneity precluded quantitative pooling of the five homogeneous ACV-only trials; qualitative synthesis indicates a consistent 0.5–3-day reduction in lesion duration.

Comparative Analysis with Alternative Agents

Among adjunctive or alternative interventions, low-level laser therapy stood out for its rapid symptomatic control: in a 60-patient RCT it shaved about 1.2 days off the total healing time and cut pain by roughly 1.1 days compared with acyclovir cream, although its practicality is limited by the need for specialised equipment [4]. Adding topical honey to the standard oral acyclovir regimen offered an even more impressive clinical edge—children recovered almost three days sooner and required fewer analgesics, a benefit achieved with an inexpensive and widely available agent [1]. Combining acyclovir with a potent topical corticosteroid (e.g., clobetasol) produced a synergistic effect; participants in an 80-patient trial healed 2.2 days faster and showed markedly less crusting than those on acyclovir alone [2]. Finally, reformulating acyclovir into muco-adhesive nanofibre patches enhanced drug retention: across two RCTs these patches delivered consistently better symptom relief—particularly for burning and itching—though improvements in overall healing time were variable [2, 3].

Safety Profile & Contra-indications

Across 634 trial participants, only transient burning or dryness were reported with topical ACV. No systemic toxicity occurred. Contra-indications are limited to known ACV or valacyclovir hypersensitivity [9].

Discussion

Evidence quality is moderate: well-conducted RCTs exist, but sample sizes remain < 100 and endpoints vary. ACV's antiviral action alone yields modest clinical gains; combining anti-inflammatory (steroids, honey) or physical (laser) modalities consistently augments outcomes. Nanotechnologies improve pharmacokinetics but require cost-effectiveness studies. No data support ACV for aphthous ulcers or autoimmune mucositis.

Clinical Recommendations & Future Directions

- **Primary herpetic gingivostomatitis** – initiate oral ACV within 72 h; consider honey rinse adjunct in children (Grade B).
- **Recurrent labial/oral HSV** – ACV cream at prodrome; laser or ACV-clobetasol nanofibre for rapid resolution (Grade B).
- **HSCT/chemotherapy patients** – prophylactic oral ACV 400 mg b.i.d. to reduce oral mucositis and HSV reactivation (Grade A).
- Research priorities: multi-centre trials standardising time-to-full-epithelialisation, head-to-head comparisons of carriers, and exploration of ACV in non-HSV inflammatory ulcers.

Conclusions

Topical and locally delivered ACV remains safe and effective for HSV-related oral lesions. Novel muco-adhesive carriers and combination regimens provide clinically meaningful accelerations in healing. Adoption of harmonised trial outcomes will enable future meta-analyses and refined guidelines.

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