

Making the most of episodic antiviral therapy for genital herpes

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Over the past 12 years there have been no new drugs licenced for the treatment of uncomplicated genital herpes (GH) infection. What clinicians have instead seen is a refinement in the doses of the various agents used and an extension of these therapies into areas of management of herpes simplex virus (HSV) that were hitherto unexpected. Sentinel studies have not just defined the benefits of therapy but also its limitations. We now accept that nucleoside analogues aciclovir (ACV), penciclovir and their prodrugs, although highly effective, cannot shut down all HSV replication: they may only limit transmission partially and their use at any stage of infection at even a high dose will not alter the natural history of disease off therapy. Despite this ACV, valaciclovir (VACV) and famciclovir (FAMCV) have a central role in the management of acquisition episodes of GH and when used continuously as suppressive therapy will control most of the clinically recurrent disease and much of the associated asymptomatic and subclinical shedding. Such therapy is associated with clear improvements in psychosocial well-being, and may be used to manage unwarranted HSV linked iatrogenic risks in pregnancy. Importantly the doses required to obtain and sustain these benefits for first episode and suppressive disease are generally agreed on.

The situation for episodic therapy is somewhat different. Early trials of episodic low dose ACV therapy conducted in a similar fashion to those for acquisition HSV episodes were relatively disappointing, showing only a limited impact on measures of healing and symptoms with no clear evidence of an ability to stop lesions progressing to a blister stage if treated early. Despite these limited benefits, ACV obtained a 5-day licence for episodic therapy and subsequent antiviral trials have until recently seen this as the standard of care.

Studies of herpes labialis infection were until recently considerably ahead of work for GH. Spruance *et al.* had shown relatively early on that for labial lesions with HSV1 all of the damage sustained with a recurrence occurred within the first 24–48 h.¹ From treatment studies, it was clear that therapy for labialis if delayed beyond the 24–48 h window was no more effective than placebo.² Shedding studies (many taken from the placebo arm of traditional 5-day treatment studies for GH) also indicate that viral shedding in GH is short lived, peaks early and rarely lasts beyond 3 days.³

Had these features been better understood at an earlier stage, the development of episodic therapy may well have been quicker and clearer than the relatively stuttering pace we have seen. With the above model it is clear that patient initiated episodic (PIE) therapy is the only strategy likely to result in any appreciable

impact on disease. PIE is likely to make little difference if initiated after lesions have developed or been present for 24–48 h; patients would also need to carry therapy with them so as to initiate treatment in the earliest stages of a recurrence. The value of extending therapy beyond the phases of lesion development and peak viral shedding would also be questionable and a fuller appreciation of this should have led to short and ultra-short therapy studies being performed much earlier.

All three orally available antiviral agents have now been studied in PIE trials of short or ultra-short treatment. Across the various trials we have compelling evidence that short duration therapies are as effective as standard 5-day regimens. To date, when head-to-head studies of agents have been performed, no advantage has been shown for one agent over another. In addition, high dose therapy for 3-day, 2-day or even 1-day (with the right drug at the correct dose) results in lesion abortion and significant shortening of disease symptoms and signs. To date, ACV 800 mg three times daily for 2 days, VACV 500 mg twice daily (bd) for 3 days or FAMCV 1 g bd for 1 day have all been shown to abort lesions and hasten lesion healing.^{4–7}

The clear benefits of a very high dose 1-day regimen leaves clinicians wondering whether doses of prodrugs can be further reduced while maintaining the advantages and convenience of ultra-short dosing periods. In this edition of *Sexual Health*, Bodsworth *et al.*⁸ show that a standard episodic pack of FAMCV (1.25 g), if taken over three doses, shows equivalence to standard 5-day therapy for the principal efficacy endpoint of proportion of healed lesions at 5.5 days. This trial challenges many of the orthodoxies surrounding this area of research with a novel design, limited patient assessment, and the inclusion of HIV-positive participants. Not all these innovations have been successful: the trial found extremely low levels of lesion abortion in all arms of the study – a probable artefact of trial design. However, there is unlikely to be any disadvantage from using FMCV in this way over the standard 5-day regimen.

There is a growing weight of evidence that episodic therapies should not be used for 5 days. PIE can be safely and effectively reduced to 1–3 days depending on the regimen or drug chosen and clinicians should challenge the use of traditional longer courses of therapy. National and international guidelines need to be updated to reflect these developments. Some barriers to the wider adoption of short and ultra-short regimens are difficult to deal with – in particular the failure of many companies producing antivirals to act on the trial evidence and alter medication pack sizes, pack inserts and the associated

pharmacy advice which still only supports traditional low dose 5-day regimes. The decision not to market, produce or promote these shorter and often smaller doses in many countries is possibly based on commercial considerations; it is difficult to envisage a company promoting the use of less of its agent to manage disease and the mechanisms for modifying the prescribing patterns for generic drugs is unclear. Until these structural problems are dealt with, clinicians need to take even greater care that effective and economical treatments, that are unobtrusive as possible, are made available to GH patients.

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