

## Objectives

Genital herpes is one of the most common sexually transmitted diseases, affecting millions of people worldwide [1]. It results from infection with the herpes simplex virus HSV-1 or HSV-2 [2]. HSV-2 antibody prevalence in the general population of developed countries is 15–25% [3]. 20–50% of patients with HSV-2 have recurrent flares [4]. Recurrent genital herpes (RGH) is associated with major medical and psychosocial morbidities [5,6].

During a herpes outbreak viral replication at the cutaneous site of inoculation leads to lesion formation characterised by sores or ulcers. The period of actual viral replication is particularly active in the first 12 hours of an episode [7].

Previous research has shown that the antiviral, famciclovir, is effective in reducing the severity and duration of episodic outbreaks of RGH [8]. Early studies of antiviral therapy for herpes simplex suggested that treatment should begin as soon as possible after the patient was aware of an outbreak, to maximise efficacy [9]. This has influenced information given to patients. However, little research has been conducted into the relation between promptness of antiviral therapy after first noticing symptoms and subsequent outbreak severity and healing time.

## Aim

The aim of the study was to conduct secondary analysis of trial data to determine whether taking famciclovir within twelve hours of first perceiving the symptoms of genital herpes is related to decreased outbreak severity and improved healing.

## Methods

Analyses were conducted on data derived from a double-blind, randomised, active-controlled study of patient-initiated therapy comparing a 2-day regimen of famciclovir with a 5-day regimen (total dose 1,250 mg in both arms) in adults with recurrent genital herpes [10].

Australian participants who completed the Herpes Symptom Checklist (HSC) [11] were selected for study from the larger trial dataset.

Patients were provided with the study medication and instructed to take the first dose as soon as possible after the next appearance of a genital herpes lesion or onset of typical prodromal symptoms heralding the likely development of one.

Patients were asked to complete a diary to document the time at which they first noticed a lesion or prodromal symptoms and the time at which they took their medication.

Patients completed the HSC on each day of the five day study period. The HSC is a 13-item measure of herpes symptoms (tingling, burning, pain, itching, tiredness, etc) and is used to rate the presence and severity of symptoms on the day of completion. Total scores range from 0 to 39 with high scores indicating greater symptomatic impact.

Tests were conducted to assess whether there were differences in HSC scores for patients who took their medication within 12 hours or after 12 hours of first perceiving their symptoms (Mann-Whitney U-tests).

The proportion of patients healed (without lesions as assessed by a clinician) at day 5 was determined. Healing at day 5 was assessed in relation to the time of taking the medication (within 12 hours or after 12 hours of noticing symptoms (Chi<sup>2</sup> test)). The odds ratio was also calculated to determine the effect size (proportion of patients healed if medication consumed within 12 hours of noticing symptoms divided by the proportion of patients healed if medication was consumed after 12 hours).

## Results

Of the 501 available patients 6 were removed due to incomplete data. Patient demographic information is shown in Table 1 and their disease information in Table 2.

Table 1: Demographic information

Age (years)	Mean (SD)	39.2 (11.6)
	Range	18 – 79
Gender	Male	292 (59%)
	Female	203 (41%)
Race	Caucasian	449 (90.7%)
	Asian	36 (7.3%)
	Other	10 (2.0%)

Table 2: Disease information

HSV duration (Years)	Mean (SD)	7.6 (8.3)
	Range	0.8 – 39.5
Number of outbreaks (previous 12 months)	< 3	58 (11.7%)
	3–9	313 (63.2%)
	≥ 10	84 (17.0%)
	Missing	40 (8.1%)
Symptom-to-treatment time lapse	Started < 12 hours	409 (82.6%)
	Started ≥ 12 hours	86 (17.4%)

Figure 1 shows HSC scores for patients over the five day study period categorised by whether patients administered their medication within 12 hours or after 12 hours of noticing symptoms of a genital herpes outbreak.

For the combined 2 and 5-day famciclovir treatment groups, patients who administered their medication within 12 hours had lower HSC scores on day 1 (within 12 hours, median HSC=6; above 12 hours, median HSC=8; Mann-Whitney U=12,733.5, p<0.05).

Patients who administered their medication within 12 hours also had lower HSC area under the curve for the five day study period (AUC; within 12 hours, median HSC=3.8; above 12 hours, median HSC=5.1; Mann-Whitney U=12,751.0, p<0.05).

Significant differences were not apparent for the treatment groups separately.

Figure 1: HSC scores for patients over the 5 day study period for combined 2 and 5-day famciclovir treatment groups, for those who administered their medication i) within 12 hours, or ii) after 12 hours of noticing symptoms

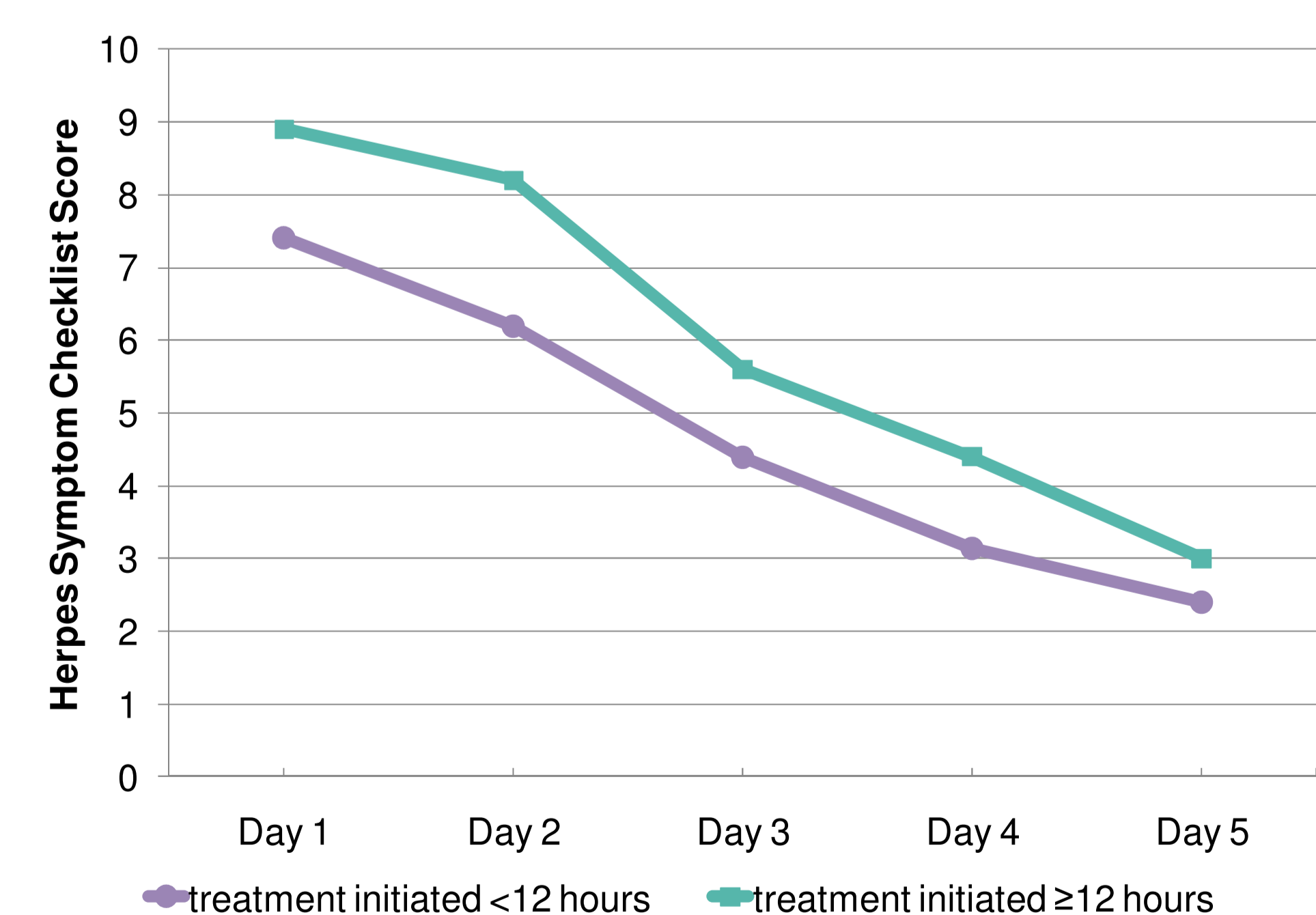


Figure 2 shows the proportion of patients (for the combined 2 and 5 day famciclovir treatment group) who were healed at day 5 dependent on whether patients took their medication within 12 hours or after 12 hours of noticing genital herpes symptoms. Figure 3 shows the same data for the 2-day treatment group only.

There was a statistically significant association between the time at which patients took their medication and healing at day 5 for the combined 2 and 5-day regimen group (Chi-square=4.95, p<0.05). Participants were 1.7 times more likely to be healed if they administered their medication within 12 hours.

This finding was also observed for the 2-day treatment group (Chi-square=6.11, p<0.05) but not for the 5-day treatment group (Chi-square=0.49, p=0.48). For the 2-day treatment group participants were 2.5 times more likely to be healed if they administered their medication within 12 hours.

Figure 2: Proportion of patients healed/not healed at day 5 for those who took their medication i) within 12 hours, or ii) after 12 hours of first noticing symptoms for the combined 2 and 5-day famciclovir treatment group

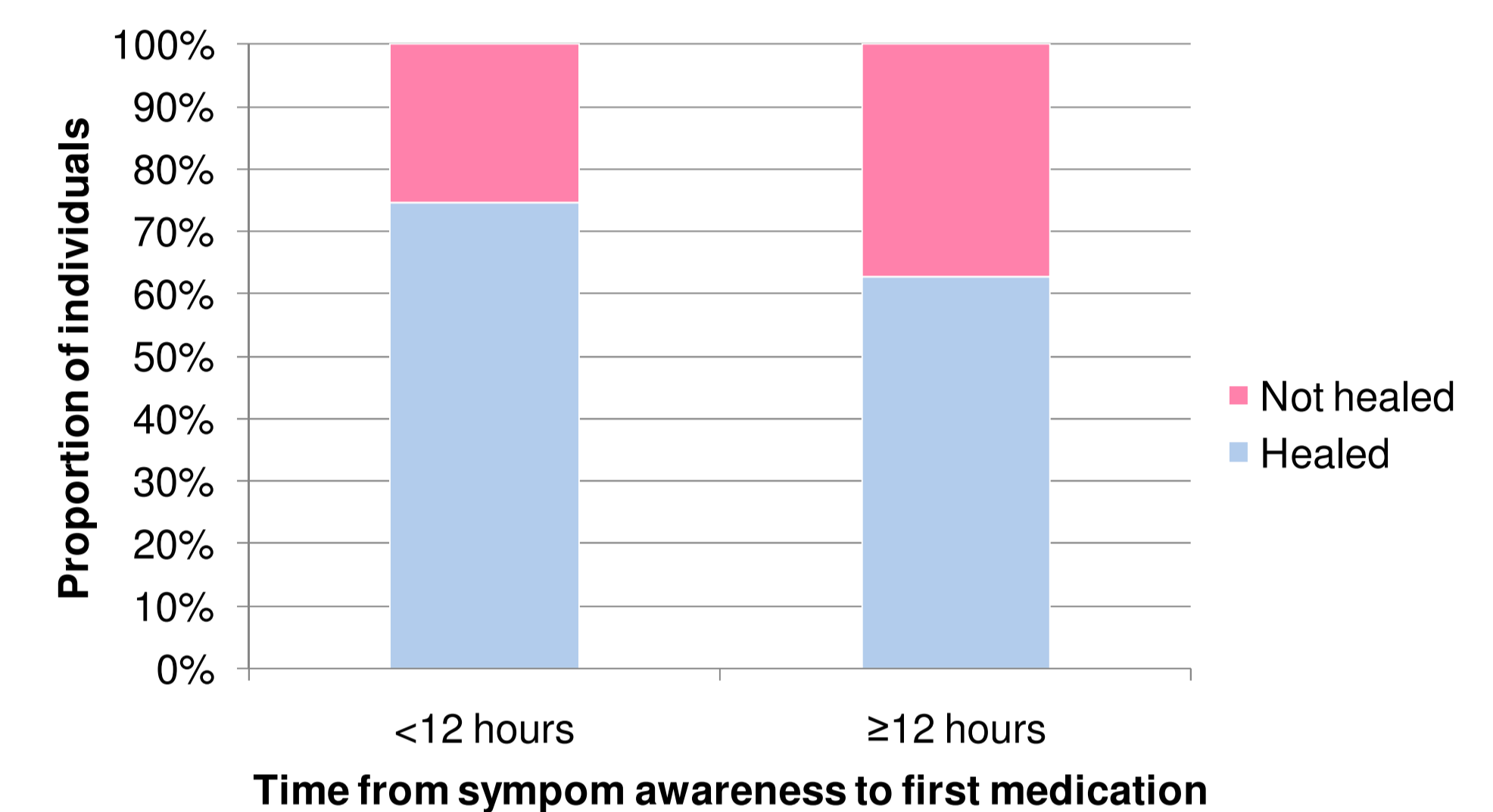
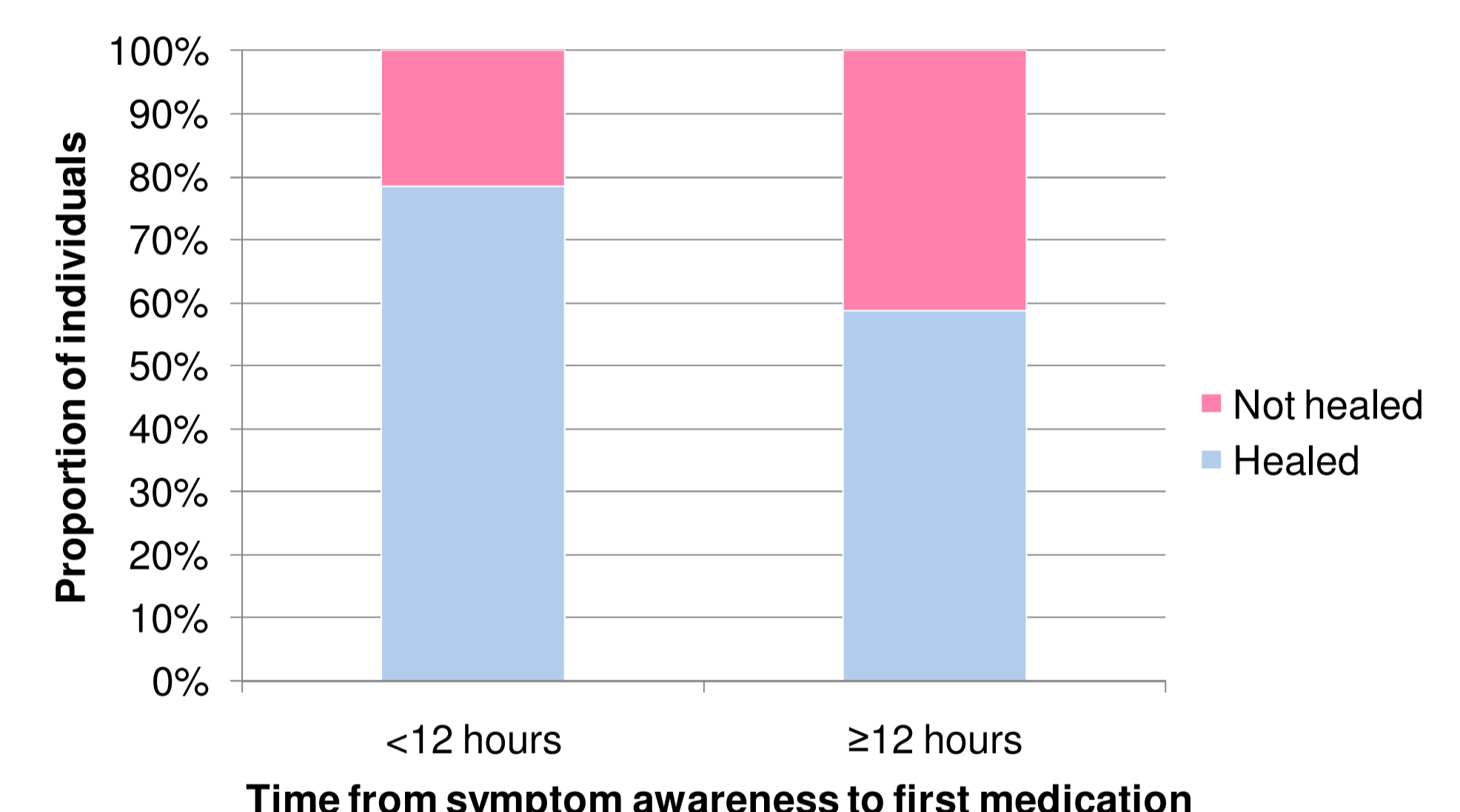


Figure 3: Proportion of patients healed/not healed at day 5 for those who took their medication i) within 12 hours, or ii) after 12 hours of first noticing symptoms for the 2-day famciclovir treatment group



## Conclusions

Administration of famciclovir within 12 hours of first becoming aware of the symptoms of a genital herpes outbreak is associated with reduced symptom severity and quicker healing.

The 2-day treatment regimen, when administered within 12 hours, is associated with a significantly higher rate of healing by day 5 than the 5-day course of treatment.

## Clinical Implications

Patients receiving famciclovir for the treatment of RGH should take their medication as soon as possible after first noticing symptoms.

The 2-day short course regimen of famciclovir may be particularly effective at reducing healing time after a symptomatic outbreak of genital herpes.

## Sponsorship

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