

# Citation Classics of Herpes Simplex Virus in 5 High-Impact General Medical Journals, 1970-2012

Aram A. Namavar<sup>1</sup>, Amanda H. Loftin<sup>2</sup>, and Hannah N. Bell<sup>3</sup>

<sup>1</sup>Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles; <sup>2</sup>Department of Orthopedic Surgery, David Geffen School of Medicine, University of California, Los Angeles; <sup>3</sup>University of California, Los Angeles, CA, USA

**Citation analysis remains one of the prominent mechanisms to determine which scholarly work has exerted the most influence on the scientific community. Article citation counts are catalogued to help identify landmark papers [1]. This study aims to provide citation classics pertaining to the Herpes Simplex Virus in order to review well-developed areas of research in dermatology. The authors conducted a search of the Thomson Reuter's Science Citation database using five high-impact general medicine journals. The top 100 articles pertaining to the Herpes Simplex Virus research from 1970 to 2012 were identified for their contribution to the field and were analyzed based on publication topic, number of citations, publication date, type of article, and country of origin. *Journal of Nature and Science*, 1(8):e146, 2015.**

Bibliometry | Herpes Simplex Virus | HSV | Citation Classics | Bibliometric Analysis

## Introduction

Articles that have value are often cited in subsequent manuscripts. These referenced papers are catalogued in bibliometric resources, such as the Thomson Reuter Science Citation Index, that track the number of times a paper is cited. As the vast majority of published articles are never referenced even once, those that are cited often have significant influence [1]. The more often an article is cited, the more likely it is to have impacted the field of dermatology and patient care [2]. The argument is that preeminent papers will receive more citations; therefore, a popular and convenient method for assessing the impact of an article is to count its citations. Further, citation analysis correlates to a measurement of the H-index, which is often used by many departments to measure not only the total number of publications, but also the quality and impact of the publication [3]. Though total number of publications is the most commonly used measurement to evaluate scholarly activity, H-index is advantageous because it takes into account the number of times the publication has been cited as well as the number of articles a faculty member has published [4].

Primary sources for up-to-date information pertaining to the field of medicine are general medical journals, namely the five highest-impact journals: *New England Journal of Medicine (NEJM)*, *The Lancet*, *the Journal of the American Medical Association (JAMA)*, *British Medical Journal*, and *Annals of Internal Medicine* (Table 1). These journals contain research from a wide variety of specialty and subspecialty studies including general clinical research, basic science studies, as well as population based research. Herpes Simplex Virus (HSV) is one of the top five most published dermatologic topics, which coincides with the fact that HSV is also one of the top ten dermatologic diagnoses made by internists [5]. Approximately 90% of individuals worldwide have one or both serotypes of Herpes Simplex Virus. HSV Type 1 is the more common serotype, with 65% of individuals in the United States having antibodies to HSV-1 [6].

The authors performed a citation analysis of Herpes Simplex Virus articles published in these journals, with the aim of highlighting landmark papers from 1970 to 2012. The characteristics of papers with high readership generate discourse and aid clinicians and scientists in directing investigations to areas of study, which may have far reaching implications in their respective fields.

For this study, "citation classics" are those articles determined to have been cited or referenced more than 100 times [7-10]. Several

journals actually publish their own citation classics and to date, a comprehensive list of the citation classics in Herpes Simplex Virus research is not available [11,12].

## Methods

The authors evaluated the aforementioned five high-impact general medical journals and conducted an extensive search of the Thomson Reuter Science Citation Index. All types of publications (original research, case reports, review articles, meta-analyses, editorials, etc.) from 1970 to 2012 were eligible for inclusion in the study. If an article dealt with more than one topic, the topic that best fit the primary objective of the article was chosen. The remaining articles were subsequently reviewed for eligibility by two independent investigators. If only one of the investigators deemed an article eligible, it was not included. The eligible articles were then sorted in descending order on the basis of the number of citations. Analysis was completed for the top 100 citation classics pertaining to Herpes Simplex Virus; however, the top 10 are illustrated in Table 2. The search was limited to the subject category of "Herpes Simplex Virus" in PubMed. Every article that had 100 or more citations was reviewed by two independent investigators and included if the topic of Herpes Simplex Virus was met. A consensus was achieved for all articles included.

The top 100 highly cited articles were then analyzed according to the following predefined items: publication topic, number of citations, publication date, type of paper (e.g., basic science, observational study), and country and institution of origin.

## Data Analysis:

The researchers reviewed and evaluated all data using standard protocols. All quantitative analyses were performed in Excel 2010 (Microsoft Corp., Redmond, WA).

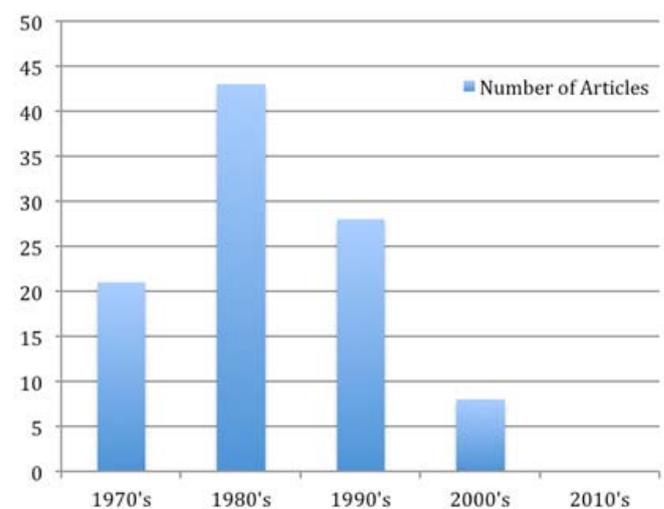


Figure 1. Number of 100 Most Cited Articles Published by Decade.

Conflict of interest: No conflicts declared.

\* Corresponding Author. Email: ANamavar@mednet.ucla.edu

© 2015 by the Journal of Nature and Science (JNSCI).

**Table 1.** Journals selected for screening.

<i>New England Journal of Medicine (NEJM)</i>	<i>The Lancet</i>
<i>Journal of the American Medical Association (JAMA)</i>	<i>British Medical Journal</i>
<i>Annals of Internal Medicine</i>	

**Table 2.** The top 10 citation classics in Herpes Simplex Virus Research

Rank	Reference	Major Findings	Number of Citations
1	13	Four homosexual men presented with gradually enlarging perianal ulcers, from which herpes simplex virus was cultured. Each patient had a prolonged course characterized by weight loss, fever, and evidence of infection by other opportunistic microorganisms including cytomegalovirus, <i>Pneumocystis carinii</i> , and <i>Candida albicans</i> .	1,057
2	25	Since the late 1970s, the prevalence of HSV-2 infection has increased by 30 percent, and HSV-2 is now detectable in roughly one of five persons 12 years of age or older nationwide.	778
3	26	The natural course of herpes simplex encephalitis is malignant. Death supervenes in a majority of cases, 70 percent in this study. Adenine arabinoside alters the course of infection in favor of survival.	630
4	27	Six of seven patients, herpes-simplex virus was recovered from trigeminal ganglions obtained at autopsy from unselected cadavers less than 12 hours after death and maintained in culture for 10 to 45 days. The results indicate that herpes-simplex virus is present in a high proportion of human trigeminal ganglions and suggest this as a possible site of latent virus causing recurrent oral infection.	568
5	28	Genital herpes simplex virus infection is a disease of growing public health importance. There are major gaps in understanding the pathogenesis and natural history of this infection. Available data suggest that in some groups a decrease in the age-specific prevalence of oral-labial herpes simplex virus and an increase in the age-specific prevalence of genital herpes simplex virus infections may be occurring simultaneously.	554
6	29	Randomly assigned 208 patients who underwent brain biopsy for presumptive herpes simplex encephalitis to receive either vidarabine (15 mg per kilogram of body weight per day) or acyclovir (30 mg per kilogram per day) for 10 days. Concluded that acyclovir is currently the treatment of choice for biopsy-proved herpes simplex encephalitis.	501
6	30	Conducted a double-blind, placebo-controlled study of acyclovir prophylaxis against infection with herpes simplex virus (HSV) in 20 seropositive recipients of bone-marrow transplants. Acyclovir appears to be a potent inhibitor of HSV replication. Although acyclovir does not appear to eradicate latent infection, it can provide effective prophylaxis against reactivated infections.	501
7	17	Paper was the first to describe Herpes Simplex Virus.	439
8	31	With the aim of improving early diagnosis of herpes simplex encephalitis a polymerase chain reaction (PCR) assay with two "nested" primer pairs was developed for the amplification of herpes simplex virus DNA in cerebrospinal fluid (CSF). The PCR result remained positive in samples drawn up to 27 days after the onset of neurological symptoms. This method is a rapid and non-invasive means to diagnose herpes simplex encephalitis; it is highly sensitive and specific.	434
9	32	This article outlined the clinical spectrum of HSV infections and review some aspects of the molecular biology, pathogenesis, therapy, and potential for prevention of these infections.	433
10	33	This paper shows declines in HSV-2 seroprevalence, suggesting that the trajectory of increasing HSV-2 seroprevalence in the United States has been reversed. Seroprevalence of HSV-1 decreased but the incidence of genital herpes caused by HSV-1 may be increasing.	419

## Results

The top 10 citation classics in Herpes Simplex Virus research from 1970 to 2012 are listed in Table 2. The most cited (1,057 citations) research was "Severe Acquired Immunodeficiency in male-homosexuals, manifested by chronic perianal ulcerative herpes-simplex lesions" [13]. The majority of the 100 most-cited articles were published during the 1970s and 1980s. After an assessment of the number of landmark papers published over time, peaks (i.e., greater than or equal to six landmark papers) were noted in the following years: 1973, 1979, 1982, 1983, 1989, and 1991 (Figure 1), which may correspond to periods of scientific advancement pertaining to HSV research. The three most common topics discussed in the literature were: Genital Herpes-Simplex Virus (18 papers), Acyclovir (17 papers), and Acquired Immunodeficiency Virus (14 papers) (Table 3). Of the 100 publications chosen for analysis, 94 were original research papers while 6 were review papers. Citations per article ranged from 1,057 to 99. Furthermore, the leading countries of origin were the U.S. (n=88) followed by the U.K. (n=6) and Sweden (n=2) (Table 4). The author of the most cited article is Frederick Siegal, M.D. He

holds no other authorships on the list. The individual listed as first author on the most number of papers on this list is Richard J. Whitley, M.D. He has authorship on eight studies and was cited as an additional author on two papers. Both of these authors are from the United States.

## Discussion

In medical literature, the number of citations of an article is one valuable measure of the influence that it either has or had on the topic it deals with. This number has, therefore, become a valued instrument in the assessment of the authors and/or the journals [14]. This type of analysis is widespread and has been reported in other areas of medicine [8,9,14-16].

Our aim in performing this citation analysis was to determine which published articles pertaining to Herpes Simplex Virus research have exerted the most influence on the specialty. By ranking the 100 most cited works, we hoped to illuminate landmark research in dermatology pertaining to studies and clinical implications of the treatment of HSV.

**Table 3.** Most Common Topic in 100 Most Cited Articles Regarding Herpes Simplex

Topic:	Year of Publication:	Number of Articles:
Acquired Immunodeficiency	1981, 1989, 1988, 1991, 2008, 2007, 2008, 1981, 1989, 1994, 1995, 1982, 1998, 1975	14
Genital Herpes-Simplex Virus	1983, 1984, 2000, 1981, 1982, 1987, 1984, 1981, 1998, 1987, 1992, 1984, 1994, 1989, 1983, 1995, 1988, 1999	18
Acyclovir	1986, 1981, 1984, 1984, 1982, 1990, 1983, 1982, 2008, 1984, 1991, 1984, 1981, 1996, 1984, 1998, 1983, 1988, 1982	17
Neonatal Herpes-Simplex Virus	1991, 1991, 1991, 1987, 1986, 1973, 1983, 1978, 1988	9
Encephalitis	1977, 1986, 1991, 1984, 1981, 1982, 1990, 1989, 1982, 1980, 1970	11
Acyclovir- Resistant Herpes-Simplex Virus	1989, 1982, 1991, 1982, 1989, 1989	6
Human Trigeminal Ganglia	1973, 1987, 1974, 1978	4
Vidarabine	1986, 1984, 1981, 1991, 1991	5
Seroprevalency/Seroepidemiology	2006, 1989, 1983, 1992	4
Pregnancy	1997, 1992, 1985	3
Bell's Palsy	1996, 1972, 1975	3
Foscarnet	1991, 1989	2
Transmission	2001, 1978	2
Human- Leukocyte Interferon	1979, 1979	2
Alzheimer's Disease	1997	1
Pneumonia	1982	1
Caesarean Delivery	2003	1
PhotoDynamic Inactivation	1973	1
Acycloguanosine	1979	1
Prostaglandins	1976	1
Peniclovir	1997	1
Vaccine	1995	1
Genome	1979	1
Famicyclovir	1998	1
Lymphocytic Meningitis	1994	1

**Table 4.** Country of Origin of Top 100 Cited Papers on Herpes Simplex Virus:

Country of Origin	Number of Publications:
United States	88
England	6
Sweden	2
Japan	1
Tanzania	1
Scotland	1
Canada	1

The results show that the citation classics occurred in the midst of a new wave of research activity related to Herpes Simplex Virus [17]. Per our analysis, the majority of research activity that produced landmark papers occurred in the 1970s and early 1980s. The year 1991 corresponded to a period of advancement in neonatal herpes simplex virus infection and predictors of mortality and morbidity due to a response to a new category of cases.

One of the most common topics published in the field was the discovery of Acyclovir, an acyclic guanosine analog that binds viral DNA polymerase, acting as a chain terminator and ending replication. Its mechanism of action necessitates early administration because replication may end as soon as 48 hours into a recurrence [18]. It has been a safe and extremely well-tolerated drug, with data from more than 35 million patients having been consistent and reassuring [19]. With that staggering number of patients, it is no surprise that the treatment of this virus would be one of the most cited publications during the assessed period. Six of the top 100 citation classics published in general medical journals during the study period pertained to Acyclovir-Resistant Herpes-Simplex Virus. Subsequent studies shortly after Acyclovir was discovered in the 1970s dealt with the discovery of HSV strains that were resistant to it [20]. These six classics were published in 1982 (2 articles), 1989 (3 articles), and 1991 (1 article).

The data indicates that most authors on the list are from the United States. Similar reviews of Anesthesia, Plastic Surgery, Emergency Medicine, General Surgery, and Orthopedic Surgery have shown that the United States contributes 70% or more of the

most cited articles to each of these specialties [8,21-23]. This may suggest that the United States is very active not only in these areas of research but also in Herpes Simplex Virus studies.

#### Study Limitations:

Access to journal articles may have been limited by the university's subscriptions. Any landmark paper published prior to 1970 was not included for analysis due to database limitations, which likely excluded some true "classic" articles.

The search was specifically for "Herpes Simplex Virus"; any reference to "HSV" was not considered if there was no prior exact match with "Herpes Simplex Virus". Articles that addressed multiple topics were categorized under one topic, upon review by two independent investigators. All findings simply indicate a correlative rather than a causal relationship.

Older published articles have the natural advantage of having more time to gain citations [24]. This may explain why most of the articles on our list are from the 1970s and 1980s. Conversely, knowledge is surpassed by newer knowledge; even true "classics" naturally lose the spotlight position over time and gradually lose frequency of citations, a phenomenon known as "obliteration by incorporation" [11].

#### Future Direction

Future studies will employ and improve upon the methodologies of citation analysis in order to define intellectual milestones in other pertinent areas of dermatology research. Moreover, the H-index

may be used to ascertain which institutions have contributed the most significant work to HSV research.

### Conclusion:

Our analysis of the most cited articles in Herpes Simplex Virus research is worthwhile for many reasons. The study demonstrates that HSV research is an important component of the field of dermatology as well as general medicine and will continue to provoke thinking in the community. We have illuminated trends in

HSV research, in particular the 21<sup>st</sup> century, which has seen a surge driven by the search for novel pharmacotherapies and the establishment of two serotypes of the virus.

### Author Contributions

Ms. Loftin, Ms. Bell, and Mr. Namavar have shared first authorship. Ms. Loftin, Ms. Bell, and Mr. Namavar had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

- [1] Tripathi RS, Blum JM, Papadimos TJ, Rosenberg AL. A bibliometric search of citation classics in anesthesiology. *BMC Anesthesiology*. 2011. Retrieved from <http://www.biomedcentral.com/1471-2253/11/24>
- [2] Bhandari, M, et al. Factors associated with citation rates in the orthopedic literature. *Can J Surg*. 2007. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2384258/?tool=pubmed>
- [3] Akl, Elie A, Joerg J Meerpohl, Dany Raad, Giulia Piaggio, Manlio Mattioni, Marco G Paggi, Aymone Gurtner, et al. "Effects of Assessing the Productivity of Faculty in Academic Medical Centres: A Systematic Review." *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne* 184, no. 11 (August 7, 2012): E602–612. doi:10.1503/cmaj.111123.
- [4] Svider, Peter F, Kevin M Mauro, Saurin Sanghvi, Michael Setzen, Soly Baredes, and Jean Anderson Eloy. "Is NIH Funding Predictive of Greater Research Productivity and Impact among Academic Otolaryngologists?" *The Laryngoscope* 123, no. 1 (January 2013): 118–22. doi:10.1002/lary.23659.
- [5] Feldman SR, Fleischer AB, McConnell C. Most common dermatologic problems identified by internists, 1990-1994. *Arch Intern Med* 1998;158(7):726-30. Retrieved from <http://archinte.jamanetwork.com/article.aspx?articleid=191779>
- [6] Wald, A, Corey, L. Epidemiology of HSV-1 and HSV-2. Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK47447/>
- [7] American Academy of Orthopaedic Surgeons. Available at <http://www.aaos.org/research/guidelines/guide.asp>. Accessed April 23, 2010.
- [8] Baltussen A, Kindler CH. Citation classics in anesthetic journals. *Anesth Analg*. 2004;98:443–451, table of contents.
- [9] Baltussen A, Kindler CH. Citation classics in critical care medicine. *Intensive Care Med*. 2004;30:902–910.
- [10] Callaham M, Wears RL, Weber E. Journal prestige, publication bias, and other characteristics associated with citation of published studies in peer-reviewed journals. *JAMA*. 2002;287:2847–2850.
- [11] Garfield E. 100 citation classics from the journal of the American Medical Association. *JAMA*. 1987; 257:52-9.
- [12] Picknett T, Davis K. The 100 most-cited articles from JMB. *J Mol Biol* 1999;293:171-6.
- [13] Siegal FP, Lopez C, Hammer GS, et al. Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. *N. Engl. J. Med*. 1981;305(24):1439-44. doi:10.1056/NEJM198112103052403.
- [14] Garfield E. Citation analysis as a tool in journal evaluation. *Science*. 1972 Nov 3;178(4060):471-9.
- [15] Adams AB, Simonson D. Publication, citations, and impact factors of leading investigators in critical care medicine. *Respir Care*. 2004;49:276–281.
- [16] Fan JC, McGhee CN. Citation analysis of the most influential authors and ophthalmology journals in the field of cataract and corneal refractive surgery 2000–2004. *Clin Experiment Ophthalmol*. 2008;36:54–61.
- [17] Nahmias AJ, Roizman B. Infection with herpes-simplex viruses 1 and 2. 1. *N. Engl. J. Med*. 1973;289(13):667-74. doi:10.1056/NEJM197309272891305.
- [18] Clark JL, Tatum NO, Noble SL. Management of genital herpes. *Am Fam Physician*. 1995;51:175–82.
- [19] Whitley RJ, Gnann JW. Acyclovir: a decade later. *N. Engl. J. Med*. 1992;327(11):782-9. doi:10.1056/NEJM199209103271108.
- [20] Elion GB. Acyclovir: Discovery, mechanism of action, and selectivity. *J. Med. Virol*. 1993;41(S1):2-6. doi:10.1002/jmv.1890410503.
- [21] Loonen MP, Hage JJ, Kon M. Plastic surgery classics: characteristics of 50 top-cited articles in four plastic surgery journals since 1946. *Plast Reconstr Surg*. 2008;121:320e–327e.
- [22] Paladugu R, Schein M, Gardezi S, Wise L. One hundred citation classics in general surgical journals. *World J Surg*. 2002;26:1099–1105.
- [23] Tsai YL, Lee CC, Chen SC, Yen ZS. Top-cited articles in emergency medicine. *Am J Emerg Med*. 2006;24:647–654.
- [24] Kelly A, Lefavre, Babak Shadgan, Peter J. O'Brien. *Clin Orthop Relat Res*. 2011 May; 469(5): 1487–1497. Published online 2010 October 5. doi: 10.1007/s11999-010-1604-1 PMID: PMC3069275.
- [25] Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med*. 1997;337(16):1105-1111. doi:10.1056/NEJM199710163371601.
- [26] Whitley RJ, Soong SJ, Dolin R, Galasso GJ, Ch'ien LT, Alford CA. Adenine arabinoside therapy of biopsy-proved herpes simplex encephalitis. National Institute of Allergy and Infectious Diseases collaborative antiviral study. *N Engl J Med*. 1977;297(6):289-294. doi:10.1056/NEJM197708112970601.
- [27] Baringer JR, Swoveland P. Recovery of herpes-simplex virus from human trigeminal ganglions. *N Engl J Med*. 1973;288(13):648-650. doi:10.1056/NEJM197303292881303.
- [28] Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med*. 1983;98(6):958-972. <http://www.ncbi.nlm.nih.gov/pubmed/6344712>. Accessed June 28, 2015.
- [29] Whitley RJ, Alford CA, Hirsch MS, et al. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med*. 1986;314(3):144-149. doi:10.1056/NEJM198601163140303.
- [30] Saral R, Burns WH, Laskin OL, Santos GW, Lietman PS. Acyclovir prophylaxis of herpes-simplex-virus infections. *N Engl J Med*. 1981;305(2):63-67. doi:10.1056/NEJM198107093050202.
- [31] Aurelius E, Johansson B, Sköldenberg B, Staland A, Forsgren M. Rapid diagnosis of herpes simplex encephalitis by nested polymerase chain reaction assay of cerebrospinal fluid. *Lancet (London, England)*. 1991;337(8735):189-192. <http://www.ncbi.nlm.nih.gov/pubmed/1670839>. Accessed July 14, 2015.
- [32] Corey L, Spear PG. Infections with herpes simplex viruses (1). *N Engl J Med*. 1986;314(11):686-691. doi:10.1056/NEJM198603133141105.
- [33] Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA*. 2006;296(8):964-973. doi:10.1001/jama.296.8.964.