F - Conclusiones

F. – **CONCLUSIONES**

1. La técnica de reducción del efecto citopático ha resultado ser es una técnica sencilla y útil para el estudio de la sensibilidad de los herpesvirus humanos tipos 1 y 2.
2. La técnica de reducción del efecto citopático presenta una reproducibilidad del 87%.
3. La adición del colorante vital (*dye-uptake*) en la técnica de reducción del efecto citopático añade complejidad a la técnica.
4. Los resultados obtenidos mediante la técnica de reducción del efecto citopático correlaccionan con la evolución clínica de los pacientes. El 98% de las lesiones causadas por cepas sensibles al aciclovir se resuelven con el tratamiento.
5. En nuestro estudio la frecuencia de cepas de herpesvirus humanos tipos 1 y 2 resistentes al aciclovir en pacientes inmunodeprimidos es baja (4%) y cuando se observa no es necesariamente indicativa de fallo terapéutico.
6. La técnica de reducción del número de placas, para la determinación de la sensibilidad *in vitro* de los herpesvirus humanos tipo 5 a diferentes antivíricos, es una técnica sencilla que requiere entre seis y ocho semanas lo que limita parcialmente su utilidad clínica.
7. Los resultados obtenidos mediante la técnica de reducción del número de placas correlacionan con la evolución clínica de los pacientes. Todos los cuadros clínicos ocasionados por cepas sensibles al ganciclovir y al foscarnet evolucionaron favorablemente con el tratamiento.
8. La frecuencia de cepas de herpesvirus humano tipo 5 resistentes *in vitro* al ganciclovir (4%) y al foscarnet (4%) en pacientes no tratados previamente es baja.
9. La técnica de reducción del número de placas, para la determinación de la sensibilidad *in vitro* del herpesvirus humano tipo 3 a diferentes antivíricos, es una técnica sencilla que requiere entre seis y ocho semanas lo que limita parcialmente su utilidad clínica.
10. En nuestro estudio no se ha detectado ninguna cepa de herpesvirus humano tipo 3 resistente al aciclovir o al foscarnet.
11. Nuestra experiencia confirma que no es necesaria la realización de estudios de

sensibilidad de los herpesvirus de forma rutinaria. El estudio de la sensibilidad de estos virus estaría indicado en las cepas aisladas de pacientes con alteraciones inmunológicas graves cuyas lesiones siguen evolucionando o empeoran estando en tratamiento con el antivírico.

G - Apéndice

G. - **APÉNDICE**

1. - Medios de cultivo

Medio de crecimiento de cultivo celular

MEM 10x (Medio mínimo esencial con Sales de Earle y sin glutamina) ..... 100 ml
SBF (Suero bovino fetal) ..... 100 ml
L- glutamina (2 mM) ..... 10 ml
Aminoácidos no esenciales ..... 10 ml
Penicilina-estreptomicina (400 UI/ml- 0.4 mg/ml) ..... 1 ml
Neomicina (0.03 mg/ml) ..... 1 ml
Hepes pH:7,4 ..... 30 ml
Se completa el volumen hasta 1.000 ml con agua bidestilada estéril y se ajusta a pH entre 7,2 y 7,4 con NaOH 1N.

2. - Soluciones tamponadas

Versene

ClNa ..... 16 g
ClK ..... 0,4 g
PO_4H_2K ..... 0,4 g
Na_2HPO_4 $2H_2O$ ..... 2,8 g
EDTA ($C_{10}H_{14}N_2O_8Na_2 \cdot 2H_2O$)……..... 0,4 g
Agua ..... 2000 ml
Se ajusta el pH de la solución a 7,4 y se esteriliza en autoclave a una temperatura de 121°C durante 15 minutos.

Hepes (20-25 mM)

$C_8H_{18}N_2O_4S$ ..... 119 g
Agua ..... 500 ml

Se ajusta el pH de la solución a 7,4 con NaOH 10N y se esteriliza en autoclave a una temperatura de 121°C durante 15 minutos.

Tampón fosfato

Se preparan soluciones madre.

Solución A: solución 0,2 M de fosfato de sodio monobásico (27,8 g en 1.000 ml de agua destilada).

Solución B: solución 0,2 M de fosfato de sodio dibásico (28,43 g de Na_2HPO_4 en 1.000 ml de agua destilada).

Para conseguir el pH deseado, mezclar solución A (monobásico) con solución B (dibásico) de acuerdo con las proporciones expresadas en la siguiente tabla:

A	B	pH	A	B	pH
93,5	6,5	5,7	45,0	55,0	6,9
92,0	8,0	5,8	39,0	61,0	7,0
90,0	10,0	5,9	33,0	67,0	7,1
87,7	12,3	6,0	28,0	72,0	7,2
85,0	15,0	6,1	23,0	77,0	7,3
81,5	18,5	6,2	19,0	81,0	7,4
77,5	22,5	6,3	16,0	84,0	7,5
73,5	26,5	6,4	13,0	87,0	7,6
68,5	31,5	6,5	10,5	90,5	7,7
62,5	37,5	6,6	8,5	91,5	7,8
56,5	43,5	6,7	7,0	93,0	7,9
51,0	49,0	6,8	5,3	94,7	8,0

Se esteriliza en autoclave a una temperatura de 121°C durante 15 minutos. Para preparar soluciones con diferente molaridad, diluir el volumen necesario con agua destilada.

Tampón de elución etanol-fosfato (1:1)

Se mezclan en proporción 1:1 fosfato de sodio monobásico 0,1 M y etanol al 95%.

Para preparar el fosfato de sodio monobásico 0,1 M, se diluye a partes iguales el fosfato de sodio monobásico 0,2 M (solución A), descrita en el apartado anterior, con agua bidestilada.

Para preparar el etanol al 95%, teniendo en cuenta la tabla de dilución de alcohol de Gay-Lussac, se mezclan 93,5 ml de alcohol absoluto y 6,5 ml de agua destilada para un volumen de 100 ml.

3. - Colorantes

Solución de rojo neutro (0,15%)

Se prepara tampón fosfato 0,1M a pH 6,0 partiendo de las soluciones A y B descritas en el apartado anterior. Se mezclan 87,7 ml de la solución A (fosfato de sodio monobásico 0,2 M) con 12,3 ml de la solución B (fosfato de sodio dibásico 0,2 M) hasta un volumen total de 200 ml con agua destilada. Se esteriliza en autoclave a 121°C durante 15 minutos.

Para preparar la solución de colorante se pesan 0,15 g de rojo neutro y se diluyen en 100 ml de tampón fosfato 0,1 M. Se homogeiniza bien y se filtra en filtros con poro de 0,2 μm. Se guarda en botella estéril.

Cristal violeta al 1%

Formaldehido ..... 10 ml
Ácido acético ..... 4 ml
Metanol ..... 60 ml
Agua destilada ..... 25 ml
Cristal violeta ..... 1 g

Disolver el cristal violeta en el metanol. Añadir el resto de las soluciones y mezclar totalmente. Se han de disolver completamente todos los cristales del colorante. La solución se debe guardar en una botella preservada de la luz hasta su utilización.

H - Bibliografía

H. – **BIBLIOGRAFÍA**

1. Bean B. 1992. Antiviral therapy: current concepts and practices. Clin Microbiol Rev, 5: 146-182.
2. De Clercq E. 1997. In search of selective antiviral chemotherapy. Clin Microbiol Rev, 10:674-693.
3. Hirsch MS, Kaplan JC, D'Aquila RT. 1996. Antiviral agents. En: Fields BN, Knipe DM, Howley PM, et al., eds. Virology. 3ª ed. Lippincott-Raven Publishers, Philadelphia, p. 431-466.
4. Roizman B. 1996. *Herpesviridae*. En: Fields BN, Knipe DM, Howley PM, et al., eds. Virology. 3ª ed. Lippincott-Raven Publishers, Philadelphia, p. 2221-2230.
5. Drew WL. 1990. En: Murray PR, Drew WL, Kobayashi GS, Thompson JH, eds. Medical Microbiology. Wolfe Medical Publications Ltd., p. 499-530.
6. *Family Herpesviridae*. 2000. En: Regenmortel MHV, Fauquet CM, Bishop DHL, et al., eds. Virus taxonomy. Classification and nomenclature of viruses. Seventh report of the international committee on taxonomy of viruses. Academic Press, San Diego, p. 203-225.
7. Roizman B, Sears AE. 1996. Herpes simplex viruses and their replication. En: Fields BN, Knipe DM, Howley PM, et al., eds. Virology. 3ª ed. Lippincott-Raven Publishers, Philadelphia, p. 2231-2295.
8. Whitley RJ. 1996. Herpes simplex viruses. En: Fields BN, Knipe DM, Howley PM, et al., eds. Virology. 3ª ed. Lippincott-Raven Publishers, Philadelphia, p. 2297-2342.
9. Herpesviruses. 1995. En: Jawetz, Melnick, Adelberg's, Brooks GF, Butel JS, Ornston LN, eds. Medical microbiology. Prentice-Hall International Inc., p. 358-380.
10. Herpesviruses. 1990. En: Davis BD, Dulbecco R, Eisen HN, Ginsberg HS, eds. Microbiology. J.B. Lippincott Company, Philadelphia, p. 929-945.

11. Kudo E, Shiota H, Naito T, Satake K, Itakura M. 1998. Polymorphisms of thymidine kinase gene in herpes simplex virus type 1: Analysis of clinical isolates from herpetic keratitis patients and laboratory strains. J Med Virol, 56: 151-158.
12. Gaudreau A, Hill E, Balfour HH, Erice A, Boivin G. 1998. Phenotypic and genotypic characterization of acyclovir-resistant herpes simplex viruses from immunocompromised patients. J Infect Dis, 178: 297-303.
13. Field AK, Biron KK. 1994. "The end of innocence". Revisited: resistance of herpesviruses to antiviral drugs. Clin Microbiol Rev, 7: 1-13.
14. Larder BA, Kemp SD, Darby G. 1987. Related functional domains in virus DNA polymerases. EMBO J, 6: 169-175.
15. Schmit I, Boivin G. 1999. Characterization of the DNA polymerasa and thymidine kinase genes of herpes simplex virus isolates from AIDS patients in whom acyclovir and foscarnet therapy sequentially failed. J Infect Dis, 180: 487-490.
16. Santaló M, Rabella N, Prats G, Net A. 1988. Infecciones por virus. La familia *Herpesviridae*. En: Net A, Quintana E, Benito S, eds. Infección en el paciente grave, Ediciones Doyma, S.A., Barcelona, p. 131-146.
17. Tj tta E. 1989. Herpes simplex virus (HSV1 and HSV2). En: Haukenes G, Haaheim LR, Pattison JR, eds. A practical guide to clinical virology, John Wiley & Sons, England, p. 95-99.
18. Rabella N, Muñoz C, Sala P. 1999. Infección congénita. En: Raspall F, Demestre X, eds. Tópicos en neonatología. EASO, Barcelona, p. 13-57.
19. Wood MJ. 1998. Viral infection in neutropenia–current problems and chemotherapeutic control. J Antimicrob Chemother, 41 (Suppl. D): 81-93.
20. Wingard JR. 1993. Viral infections in leukemia and bone marrow transplant patients. Leuk Lymphoma, 11 (Suppl. 2): 115-125.
21. A report from the British Society for Antimicrobial Chemotherapy Working Party on Antiviral Therapy. 2000. Management of herpes virus infections following transplantation. J Antimicrob Chemother, 45: 729-748.

22. Nash G, Ross JS. 1974. Herpetic esophagitis a common cause of esophageal ulceration. Hum Pathol, 5: 339-345.
23. Bernard E, Michiels JF, Saint-Paul MC, Keita O, Dellamonica P. 1994. Herpetic hepatitis in an AIDS patient (letter). Presse Med, 23: 140.
24. Skoldenberg B, Forsgren M, Alestig K, et al. 1984. Acyclovir versus vidarabine in herpes simplex encephalitis. Randomized, multicenter study in consecutive Swedish patients. Lancet, 2: 707-711.
25. Whitley RJ, Alford CA, Hirsch MS, et al. 1986. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med, 314: 144-149.
26. Whitley R, Arvin A, Prober C, et al. 1991. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. N Engl J Med, 324: 444-449.
27. Mindel A, Adler MW, Sutherland S, Fiddian AP. 1982. Intravenous acyclovir treatment for primary genital herpes. Lancet, 1; 697-700.
28. Corey L, Fife K, Benedetti JK. 1983. Intravenous acyclovir for the treatment of primary genital herpes. Ann Intern Med, 98: 914-921.
29. Peacock JE, Kaplowitz LG, Sparling PF, et al. 1988. Intravenous acyclovir therapy of first episodes of genital herpes: A multicenter double-bind, placebo-controlled trial. Am J Med, 85: 301-306.
30. Nilsen AE, Aasen T, Halsos AM, et al. 1982. Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. Lancet, 2: 571-573.
31. Bryson YJ, Dillon M, Lovett M, et al. 1983. Treatment of first episodes of genital herpes simplex virus infections with oral acyclovir. A randomized double-blind controlled trial in normal subjects. N Engl J Med, 308: 916-921.
32. Mertz GJ, Crichlow CW, Benedetti J, et al. 1984. Double-blind placebo-controlled trial of oral acyclovir in first episode genital herpes simplex virus infection. JAMA, 252: 1147-1151.
33. Corey L, Benedetti JK, Critchlow CW, et al. 1982. Double-blind controlled trial of topical acyclovir in genital herpes simplex virus infections. Amer J Med, 73:326-334.

34. Corey L, Nahmias AJ, Guinan ME, Benedetti JK, Critchlow CW, Holmes KK. 1982. A trial of topical acyclovir in genital herpes simplex virus infections. N Engl J Med, 306: 1313-1319.
35. Reichman RC, Badger GJ, Mertz GJ, et al. 1984. Treatment of recurrent genital herpes simplex infections with oral acyclovir. JAMA, 251: 2103-2107.
36. Ruhnek-Forsbeck M, Sandstrom E, Andersson B, et al. 1985. Treatment of recurrent genital herpes simplex infections with oral acyclovir. J Antimicrob Chemother, 16: 621-628.
37. Saiag P, Praindhui D, Chastang C, for the Genival Study Group. 1999. A double-blind, randomized study assesssing the equivalence of valacyclovir 1000 mg once daily versus 500 mg twicw daily in the episodic treatment of recurrent genital herpes. J Antimicrob Chemother, 44: 525-531.
38. Mindel A, Faherty A, Hindley D, et al. 1984. Prophylactic oral acyclovir in recurrent genital herpes. Lancet, 2: 57-59.
39. Mostow SR, Mayfield JL, Marr JJ, DruckerJL. 1988. Suppression of recurrent genital herpes by single daily dosages of acyclovir. Am J Med, 85: 30-33.
40. Douglas JM, Critchlow C, Benedetti J, et al. 1984. A double-blind study of oral acyclovir for suppression of recurrences of genital herpes simplex virus infection. N Engl J Med, 310: 1551-1556.
41. Mertz GJ, Jones CC, Mills J, et al. 1988. Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection. JAMA, 260: 201-206.
42. Kaplowitz LG, Baker D, Gelb L, et al. 1991. Prolonged continuous acyclovir treatment of normal adults with frequently recurring genital herpes simplex virus infection. JAMA, 265: 747-751.
43. Meyers JD, Wade JC, Mitchell CD, et al. 1982. Multicenter collaborative trial of intravenous acyclovir for treatment of mucocutaneous herpes simplex virus infection in the immunocompromised host. Am J Med, 73 (Suppl.1A): 229-235.
44. Wade JC, Newton B, McLaren C, Flournoy N, Keeney RE, Meyers JD. 1982. Intravenous acyclovir to treat mucocutaneous herpes simplex virus infection after marrow transplantation. Ann Intern Med, 96: 265-269.

45. Shepp DH, Newton BA, Dandliker PS, Flournoy N, Meyers JD. 1985. Oral acyclovir therapy for mucocutaneous herpes simplex virus infections in immunocompromised marrow transplant recipients. Ann Intern Med, 102: 783-785.
46. Saral R, Burns WH, Laskin OL, Santos GW, Lietman PS. 1981. Acyclovir prophylaxis of herpes-simplex virus infections: A randomized, double-blind controlled trial in bone-marrow-transplant recipients. N Engl J Med, 305: 63-67.
47. Saral R, Ambinder RF, Burns WH, et al. 1983. Acyclovir prophylaxis against herpes simplex virus infection in patients with leukemia. A randomized, double-blind, placebo-controlled study. Ann Intern Med, 99: 773-776.
48. Gluckman E, Devergie A, Melo R, et al. 1983. Prophylaxis of herpes infections after bone marrow transplantation by oral acyclovir. Lancet, 2: 706-708.
49. Wade JC, Newton N, Flournoy N, Meyers D. 1984. Oral acyclovir for prevention of herpes simplex virus reactivation after marrow transplantation. Ann Intern Med, 100: 823-828.
50. Seale L, Jones CJ, Kathpalia S, et al. 1985. Prevention of herpes-virus infections in renal allograft recipients by low-dose oral acyclovir. JAMA, 254:3435-3438.
51. Charmot G, Ingrand D, Simon F, et al. 1990. Infection herpétique résistante à l'aciclovir chez un malade immunodéprimé. Effet favorable du foscarnet. Presse Med, 19: 1905-1906.
52. Erlich KS, Jacobson MA, Koehler JE, et al. 1989. Foscarnet therapy for severe acyclovir-resistant herpes simplex virus type-2 infections in patients with the acquired immunodeficiency syndrome (AIDS). An uncontrolled trial. Ann Intern Med, 110: 710-713.
53. Sall RK, Kauffman L, Levy CS. 1989. Successful treatment of progressive acyclovir-resistant herpes simplex virus using intravenous foscarnet in a patient with the acquired immunodeficiency syndrome. Arch Dermatol, 125: 1548-1550.
54. Verdonck LF, Cornelissen JJ, Smit J, et al. 1993. Successful foscarnet therapy for acyclovir-resistant mucocutaneous infection with herpes simplex virus in a recipient of allogeneic BMT. Bone Marrow Transplant, 11: 177-179.

55. Safrin S, Assaykeen T, Follansbee S, Mills J. 1990. Foscarnet therapy for acyclovir-resistant mucocutaneous herpes simplex virus infection in 26 AIDS patients: preliminary data. J Infect Dis, 161:1078-1084.
56. Youle MM, Hawkins DA, Collins P, et al. 1988. Acyclovir-resistant herpes in AIDS treated with foscarnet. Lancet, 2:341-342.
57. Chatis PA, Miller CH, Schrager LE, Crumpacker CS. 1989. Successful treatment with foscarnet of an acyclovir resistant mucocutaneous infection with herpes simplex virus in a patient with acquired immunodeficiency syndrome. N Engl J Med, 320: 297-300.
58. Mocarski ES. 1996. Cytomegalovirus and their replication. En: Fields BN, Knipe DM, Howley PM, et al., eds. Virology. 3ª ed. Lippincott-Raven Publishers, Philadelphia, p. 2447-2492.
59. Stinski M. 1991. Molecular biology of cytomegalovirus replication. En: Ho M, ed. Cytomegalovirus. Biology and infection. 2ª ed. Plenum Medical Book Company, New York, p. 7-35.
60. Rasmussen LE. 1991. Gene products of cytomegalovirus and their immunologic significance. En: Ho M, ed. Cytomegalovirus. Biology and infection. 2ª ed. Plenum Medical Book Company, New York, p. 37-56.
61. Haffey ML, Field AK. 1995. Selective inhibiton of cytomegalovirus replication. En: Jeffries DJ, De Clercq E, eds. Antiviral chemotherapy. John Wiley & Sons, Chichester, p. 83-126.
62. Lurain NS, Weinberg A, Crumpacker CS, for the adult aids clinical trial group CMV laboratories. 2001. Sequencing of cytomegalovirus UL97 gene for genotypic antiviral resistance testing. Antimicrob Agents Chemother, 45: 2775-2780.
63. Acquired cytomegalovirus infection in immunocompetent patients. En: Ho M, ed. Cytomegalovirus. Biology and infection. 2ª ed. Plenum Medical Book Company, New York, p. 229-247.
64. Human cytomegalovirus infections in immunosuppressed patients. En: Ho M, ed. Cytomegalovirus. Biology and infection. 2ª ed. Plenum Medical Book Company,

New York, p. 249-300.

65. Drew, WL. Cytomegalovirus infection in patients with AIDS. J Infect Dis, 158: 449-456.
66. Collaborative DHPG Tratment Study Group. 1986. Treatment of serious cytomegalovirus infections with 9-(1,3-dihydroxy-2-propoxymethyl)guanine in patients with AIDS and other immunodeficiencies. N Engl J Med, 314: 801-805.
67. Felsenstein D, D'amico DJ, Hirsch MS, et al. 1985. Treatment of cytomegalovirus retinitis with 9-(2-hydroxy-1-(hydroxymethyl)ethoxymethyl)guanine. Ann Intren Med, 103: 377-380.
68. Holland GN, Sakamoto MJ, Hardy D, et al. 1986. Treatment of cytomegalovirus retinopathy in patients with acquired immunodeficiency syndrome. Arch Ophthalmol, 104:1794-1800.
69. Jabs DA, Enger C, Bartlett JC. 1989. Cytomegalovirus retinitis and acquired immunodeficiency syndrome. Arch Ophthalmol, 107: 75-80.
70. Laskin OL, Cederberg DM, Mills J, et al. 1987. Ganciclovir for the treatment and suppression of serious infections caused by cytomegalovirus. Am J Med, 83: 201-207.
71. Spector SA, Weingeist T, Pollard RB, et al. 1993. A randomized, controlled study of intravenous ganciclovir therapy for cytomegalovirus peripheral retinitis in patients with AIDS. J Infect Dis, 168: 557-563.
72. Drew WL, Ives D, Lalezari JP, et al. 1995. Oral ganciclovir as maintenance treatment for cytomegalovirus retinitis in patients with AIDS. N Engl J Med, 333: 615-620.
73. The oral GCV European and Australian Cooperative Study Group. Intravenous versus oral ganciclovir: European/Australian comparative study of efficacy and safety in the prevention of cytomegalovirus retinitis recurrence in patients with AIDS. AIDS, 9:471-477.
74. Dieterich DT, Kotler DP, Busch DF, et al. 1993. Ganciclovir treatment of cytomegalovirus colitis in AIDS: a randomized, double-blind, placebo-controlled multicenter study. J Infect Dis, 167: 278-282.

75. Blanshard C, Benhamou Y, Dohin E, Lernestedt JO, Gazzard BG, Katlama C. 1995. Treatment of AIDS-associated gastrointestinal cytomegalovirus infection with foscarnet and ganciclovir: A randomized comparison. J Infect Dis, 172: 622-628.
76. Fuller GN, Gill SK, Guiloff RJ, et al. 1990. Ganciclovir for lumbosacral polyradiculopathy in AIDS. Lancet, 335: 48-49.
77. Andres HJ, Weiss N, Bogner JR, Goebel FD. 1998. Ganciclovir and foscarnet efficacy in AIDS-related CMV polyradiculopathy. J Infect, 36: 29-33.
78. Shepp DH, Dandliker PS, De Miranda P, et al. 1985. Activity of 9-[2-hydroxy-1-(hydroxymethyl]guanine in the treatment of cytomegalovirus pneumonia. Ann Intern Med, 103: 368-373.
79. Winston DJ, Ho WG, Bartoni K, et al. 1988. Ganciclovir therapy for cytomegalovirus infections in recipients of bone marrow transplants and other immunosuppressed patients. Rev Infect Dis, 10 (Suppl. 3): 547-553.
80. Emanuel D, Cunningham I, Jule-Elysee K, et al. 1988. Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. Ann Intern Med, 109: 777-782.
81. Reed EC, Bowden RA, Dandliker PS, Lilleby KE, Meyers JD. 1988. Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants. Ann Intern Med, 109: 783-788.
82. Schmidt GM, Kovacs A, Zaia JA, et al. 1988. Ganciclovir/immunoglobulin combination therapy for the treatment of human cytomegalovirus-associatedintersttial pneumonia in bone marrow allograft recipients. Transplantation, 46: 905-907.
83. Ljungman P, Engelhard D, Link H, et al. 1992. Treatment of interstitial pneumonitis due to cytomegalovirus with ganciclovir and intravenous immune globulin. Experience of European Bone Marrow Transplant Group. Clin Infect Dis, 14: 831-835.

84. Aulitzky WE, Tilg H, Niederwieser D, Hackl M, Meister B, Huber C. 1988. Ganciclovir and hyperimmunoglobulin for treating cytomegalovirus infection in bone marrow transplant recipients. J Infect Dis, 158: 488-489.
85. Reed EC, Wolford JL, Kopecky KJ, et al. 1990. Ganciclovir for the treatment of cytomegalovirus gastroenteritis in bone marrow transplant patients. A randomized, placebo-controlled trial. Ann Intern Med, 112: 505-510.
86. Dunn DL, Mayoral JL, Gilligham KJ, et al. 1991. Treatment of invasive cytomegalovirus disease in solid organ transplant patients with ganciclovir. Transplantation, 51: 98-106.
87. Harbison MA, DeGirolami PC, Jenkins RL, Hammer SM. 1988. Ganciclovir therapy of severe cytomegalovirus infections in solid-organ transplant recipients. Transplantation, 46:82-88.
88. Hecht DW, Snydman DR, Crumpacker CS, Werner BG, Heinze-Lacey B and the Boston Renal Transplant Study Group. 1988. Ganciclovir for treatment of renal transplant-associated primary cytomegalovirus pneumonia. J Infect Dis, 157: 187-190.
89. Podzamczer D, Arribas JR, Mallolas J, Peña JM, Pulido F, del Grupo de Estudio del Sida (GESIDA). 2001. Tratamiento de las infecciones oportunistas en pacientes adultos y adolescentes infectados por el virus de la inmunodeficiencia humana en la era del tratamiento antirretrovírico de gran actividad. Enferm Infecc Microbiol Clin, 19: 376-392.
90. Boeckh M, Gooley TA, Myerson D, Cunningham T, Schoch G, Bowden RA. 1996. Cytomegalovirus pp65 antigenemia-guided early tretament with ganciclovir versus ganciclovir at engrafment after allogenic marrow transplantation: a randomised duble-blind study. Blood, 88:4063-4071.
91. Schmidt GM; Horak DA, Niland JC, et al. 1991. A randomized, controlled trial of prophylactic ganciclovir for cytomegalovirus pulmonary infection in recipients of allogeneic bone marrow transplants. N Engl J Med, 324: 1005-1011.
92. Goodrich JM, Mori M, Gleaves CA, et al. 1991. Early treatment with ganciclovir to prevent cytomegalovirus disease after allogenic bone marrow transplantation.

N Engl J Med, 325: 1601-1607.

93. Hibberd PL, Tolkoff-Rubin NE, Conti D, et al. 1995. Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients. A randomized controlled trial. Ann Intern Med, 123: 18-26.
94. Von Bueltzingsloewen A, Bordigoni P, Witz F, et al. 1993. Prophylactic use of ganciclovir for allogeneic bone marrow transplant recipients. Bone Marrow Transplant, 12: 197-202.
95. Winston DJ, Ho WG, Bartoni K, et al. 1993. Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients: results of a placebo-controlled, double blind trial. Ann Intern Med, 118: 179-184.
96. Goodrich JM; Bowden RA, Fisher L, et al. 1993. Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. Ann Intern Med, 118: 173-178.
97. Merigan TC, Renlund DG, Keay S, et al. 1992. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. N Engl J Med, 326: 1182-1186.
98. Leray H, Mourad G, Chong M, Segondy M, Mion C. 1995. Prophylactic treatment of cytomegalovirus primary infection with ganciclovir in renal transplant recipients. Transplant Proc, 27: 2448.
99. Cohen AT, O'Grady JG, Sutherland S, Sallie R, Tan KC, Williams R. 1993. Controlled trial of prophylactic versus therapeutic use of ganciclovir in liver transplantation in adults. J Med Virol, 40: 5-9.
100. Lumbreras C, Otero JR, Herrero JA, et al. 1993. Ganciclovir prophylaxis decreases frequency and severity of cytomegalovirus disease in seropositive liver transplant recipients treated with OKT3 monoclonal antibodies. Antimicrob Agents Chemother, 37: 2490-2492.
101. Cohen JI, Straus SE. 1996. Varicella-zoster virus and their replication. En: Fields BN, Knipe DM, Howley PM, et al., eds. Virology. 3ª ed. Lippincott-Raven

Publishers, Philadelphia, p. 2525-2545.

102. Visse B, Huraux J, Fillet A. 1999. Point mutations in the varicella-zoster virus DNA polymerase gene confers resistance to foscarnet and slow growth phenotype. J Med Virol, 59: 84-90.
103. Arvin AM. 1996. Varicella-zoster virus. En: Fields BN, Knipe DM, Howley PM, et al., eds. Virology. 3ª ed. Lippincott-Raven Publishers, Philadelphia, p. 2493-2523.
104. Overall JC. 1998. Viral infections of the fetus and neonate. En: Feigin RD, Cherry JD, eds. Textbook of pediatric infectious diseases. W.B. Saunders Company, Philadelphia, p.856-892.
105. Gershon AA. 1998. Varicella-zoster virus. En: Feigin RD, Cherry JD, eds. Textbook of pediatric infectious diseases. W.B. Saunders Company, Philadelphia, p. 1769-1777.
106. Arvin AM, Alford CA. 1990. Chronic intrauterine and perinatal infections. En: Galasso GJ, Whitley RJ, Merigan TC, eds. Antiviral agents and viral diseases of man. Raven Press, New York, p.497-580.
107. Shepp DH, Dandliker PS, Meyers JD. 1986. Treatment of varicella-zoster infection in severely immunocompromised patients: A randomized comparison of acyclovir and vidarabine. N Engl J Med, 314: 208-212.
108. Whitley RJ, Gnann JW, Hinthorn D, et al. 1992. Disseminated herpes zoster in immunocopromised host: a comparative trial of acyclovir and vidarabine. J Infect Dis, 165: 450-455.
109. Balfour HH, Kelly JM, Suarez CS, et al. 1990. Acyclovir treatment of varicella in otherwise healthy children. J Pediatr, 116: 633-639.
110. Balfour HH, Rotbart HA, Feldman S, et al. 1992. Acyclovir treatment of varicella in otherwise healthy adolescents. The Collaborative Acyclovir Varicella Study Group. J Pediatr, 120: 627-633.
111. Peterslund NA, Esmann V, Ipsen J, Christensen KD, Petersen CM. 1984. Oral and intravenous acyclovir are equally effective in herpes zoster. J Antimicrob Chemother, 14: 185-189.

112. Wood MJ, Ogan PH, McKendrick MW. 1988. Efficacy of oral acyclovir treatment of acute herpes zoster. Am J Med, 85: 79-83.
113. Haake DA, Zakowski PC,Haake DL, Bryson YJ. 1990. Early treatment with acyclovir for varicella pneumonia in otherwise healthy adults: retrospective controlled study and review. Rev Infect Dis, 12: 788-798.
114. Nyerges G, Meszner Z, Gyarmati E, Kerpel-Fronius S. 1988. Acyclovir prevents dissemination of varicella in immunocompromised children. J Infect Dis, 157: 309-313.
115. Prober CG, Kirk LE, Keeney RE. 1982. Acyclovir therapy of chickenpox in immunosuppressed children – a colaborative Study. J Pediatr, 101: 622-625.
116. Balfour HH, Bean B, Laskin OL, et al. 1983. Acyclovir halts progression of herpes zoster in immunocompromised patients. N Engl J Med, 308: 1448-1453.
117. Shepp DH, Dandliker PS, Meyers JD. 1986. Treatment of varicella-zoster virus infection in severely immunocompromised patients. N Engl J Med, 314: 208-212.
118. Tyring S, Barbarash RA, Nahlik JE, et al. 1995. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. A randomized, double-blind, placebo-controlled trial. Collaborative Famciclovir Herpes Zoster Study Group. Ann Intern Med, 123: 89-96.
119. Safrin S, Berger TG, Gilson I, et al. 1991. Foscarnet therapy in five patients with AIDS and acyclovir-resistant varicella-zoster virus infection. Ann Intern Med, 115:19-21.
120. Smith KJ, Davis C, James WD, Skelton HG, Angritt P. 1991. Acyclovir-resistant varicella-zoster responsive to foscarnet. Arch Dermatol, 127: 1069-1071.
121. Breton G, Fillet AM, Katlama C, Bricaire F, Caumes E. 1998. Acyclovir-resistant herpes zoster in human immunodeficiency virus-infected patients: results of foscarnet therapy. Clin Infect Dis, 27: 1525-1527.
122. Blum MR, Liao SHT, De Miranda P. 1982. Overview of acyclovir pharmacokinetic disposition in adults and children. Am J Med, 73: 186-192.
123. Lietman PS. 1982. Acyclovir clinical pharmacology. An overview. Am J Med, 73: 193-196.

124. Aciclovir. 1997. En: Kucers A, Crowe SM, Grayson ML, Hoy JF, eds. The use of antibiotics. A clinical review of antibacterial, antifungal and antiviral drugs. Butterworth-Heinemann, Oxford, p.1509-1541.
125. Hayden FG. 1996. Antiviral agents. En: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Goodman Gilman A, eds. Goodman & Gilman's the pharmacological basis of therapeutics. McGraw-Hill, New York, p. 1191-1223.
126. Whitley RJ, Levin M, Barton N, et al. 1984. Infections caused by herpes simplex virus in the immunocompromised host: natural history and topical acyclovir therapy. J Infect Dis, 150: 323-329.
127. De Miranda P, Good SS, Krasny HC, et al. 1982. Metabolic fate of radioactive acyclovir in humans. Am J Med, 73: 215-220.
128. Jacobson MA, Gallant J, Wang LH, et al. 1994. Phase I trial of valaciclovir, the L-valyl ester of acyclovir, in patients with advanced human immunodeficiency virus disease. Antimicrob Agents Chemother, 38: 1534-1540.
129. Soul-Lawton J, Seaber E, On N, Wootton R, Rolan P, Posner J. 1995. Absolute bioavailability and metabolic disposition of valaciclovir, the L-valyl ester of acyclovir, following oral administration to humans. Antimicrob Agents Chemother, 39: 2759-2764.
130. Steingrimsdottir H, Gruber A, Palm C, Grimfors G, Kalin M, Eksborg S. 2000. Bioavailability of acyclovir after oral administration of aciclovir and its prodrug valaciclovir to patients with leukopenia after chemotherapy. Antimicrob Agents Chemother, 44: 207-209.
131. Bean B, Aeppli D. 1985. Adeverse effects of high-dose intravenous acyclovir in ambulatory patients with acute herpes zoster. J Infect Dis, 151: 362-365.
132. Wald A, Benedetti J Davis G, et al. 1994. A randomised double-blind comparative trial comparing high and standard dose oral acyclovir for first-episode genital herpes infections. Antimicrob Agents Chemother, 38: 174-176.
133. Sawyer MH, Webb DE, Balow JE, Strauss SE. 1988. Acyclovir-induced renal failure: clinical course and histology. Am J Med, 84: 1067-1071.
134. Feder HM, Goyal RK, Krause PJ. 1995. Acyclovir induced neutropenia in an

infant with herpes simplex encephalitis case report. Clin Infect Dis, 20: 1557-1559.

135. Corey L, Benedetti J, Critchlow C, et al. 1983. Treatment of primary first episode genital herpes simplex virus infections with acyclovir, results of topical, intravenous and oral therapy. Antimicrob Agents Chemother, 12 (Suppl. B): 79-88.
136. Elion GB. 1983. The biochemistry and mechanism of action of acyclovir. J Antimicrob Chemother, 12, Suppl. B: 9-17.
137. Reusser P. 1996. Herpesvirus resistance to antiviral drugs: a review of the mechanisms, clinical importance and therapeutic options. J Hosp Infect, 33: 235-248.
138. Spruance SL, Stewart JC, Rowe NH, et al. 1990. Treatment of recurrent herpes simplex labialis with oral acyclovir. J Infect Dis, 161: 185-190.
139. Tyring SK, Douglas JM, Lawrence C, Spruance SL, Esmann J, for the Valaciclovir International Study Group. 1998. A randomized, placebo-controlled comparison of oral valacyclovir and acyclovir in immunocompetent patients with recurrent genital herpes infections. Arch Dermatol, 134: 185-191.
140. Kohl S. 1993. Treatment of herpes simplex virus infection. En: Root RK, Sande MA, eds. Viral infections: diagnosis, treatment and prevention. Churchill Livingstone Inc., New York, p. 31-55.
141. Peterslund NA, Seyer-Hansen K, Ipsen J, et al. 1981. Acyclovir in herpes zoster. Lancet, 2: 827-830.
142. Beutner KR, Friedman DJ, Forszpaniak C, Andersen PL Wood MJ. 1995. Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immmunocompromised adults. 39:1546-1553.
143. Meyers JD, Reed EC, Schepp DH, et al. 1988. Acyclovir for prevention of cytomegalovirus infection and disease after allogenic marrow transplantation. N Engl J Med, 318: 70-75.
144. Balfour HH, Chace BA, Stapleton JT, Simmons RL, Fryd DS. 1989. A randomized, placebo-controlled trial of oral acyclovir for the prevention of

cytomegalovirus disease in recipients of renal allografts. N Engl J Med, 320: 1381-1387.

145. Dunn DL, Gillingham KJ, Kramer MA, et al. 1994. A prospective randomized study of acyclovir versus ganciclovir plus human immune globulin prophylaxis of cytomegalovirus infection after solid organ transplantation. Transplantation, 57: 876-884.
146. Singh N, Yu VL, Mieles L, et al. 1994. High dose acyclovir compared with short course preemptive ganciclovir therapy to prevent cytomegalovirus disease in liver transplant recipients. A randomized trial. Ann Intern Med, 120: 375-381.
147. Legendre CM, Norman DJ, Keating MR, Maclaine GDH, Grant DM. 2000. Valaciclovir prophylaxis of cytomegalovirus infection and disease in renal transplantation: an economic evaluation. Transplantation, 70: 1463-1468.
148. Lowance D, Neumayer HH, Legendre CM, et al. 1999. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. N Engl J Med, 340: 1462-1470.
149. Morfin F, Souillet G, Bilger K, Ooka T, Aymard M, Thouvenot D. 2000. Genetic characterization of thymidine kinase from acyclovir-resistant and – susceptible herpes simplex virus type 1 isolated from bone marrow transplant recipients. J Infect Dis, 182: 290-293.
150. Saijo M, Suzutani T, Itoh K, et al. 1999. Nucleotide sequence of thymidine kinase gene of sequential acyclovir-resistant herpes simplex virus type 1 isolates recovered from a child with Wiskott-Aldrich syndrome: Evidence for reactivation of acyclovir-resistant herpes simplex virus. J Med Virol, 58: 387-393.
151. Horsburgh BC, Chen S, Hu A, Mulamba GB, Burns WH, Coen DM. 1998. Recurrent acyclovir-resistant herpes simplex in an immunocompromised patient: Can strain differences compensate for loss of thymidine kinase in pathogenesis?. J Infect Dis, 178: 618-625.
152. Boivin G, Edelman CK, Pedneault L, Talarico CL, Biron KK, Balfour HH. 1994. Phenotypic and genotypic characterization of acyclovir-resistant varicella-zoster viruses isolated from persons with AIDS. J Infect Dis, 170: 68-75.

153. Morfin F, Thouvenot D, Turenne-Tessier M, Lina B, Aymard M, Ooka T. 1999. Phenotypic and genetic characterization of thymidine kinase from clinical strains of varicella-zoster virus resistant to acyclovir. Antimicrob Agents Chemother, 43: 2412-2416.
154. Talarico CL, Phelps WC, Biron KK. 1993. Analysis of the thymidine kinase genes from acyclovir-resistant mutants of varicella-zoster virus isolated from patients with AIDS. J Virol, 67: 1024-1033.
155. Snoeck R, Gérard M, Sadzot-Delvaux C, et al. 1994. Meningoradiculoneuritis due to acyclovir-resistant varicella-zoster virus in an acquired immune deficiency syndrome patient. J Med Virol, 42: 338-347.
156. Fillet A, Dumont B, Caumes E, et al. 1998. Acyclovir-resistant varicella-zoster virus: phenotypic and genetic characterization. J Med Virol, 55: 250-254.
157. Kimberlin DW, Whitley RJ. 1996. Antiviral resistance: mechanisms, clinical significance, and future implications. J Antimicrob Chemother, 37: 403-421.
158. Faulds D, and Heel RC. 1990. Ganciclovir. A review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in cytomegalovirus infections. Drugs, 39: 597-638.
159. Jung D, Dorr A. 1999. Single-dose pharmacokinetics of valganciclovir in HIV- and CMV- seropisitive subjects. J Clin Pharmacol, 39: 800-804.
160. Brown F, Banken L, Saywell K, Arum I. 1999. Pharmacokinetics of valganciclovir and ganciclovir following multiple oral dosages of valganciclovir in HIV- and CMV- seropositive volunteers. Clin Pharmacokinet, 37: 167-176.
161. Pescovitz MD, Rabkin J, Merion RM, et al. 2000. Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. Antimicrob Agents Chemother, 44: 2811-2815.
162. Jacobson MA, Kramer F,Bassiakos V, et al. 1994. Randomised phase 1 trial of two different combination foscarnet and ganciclovir chronic maintenance therapy regimens for AIDS patients with cytomegalovirus retinitis: AIDS clinical trials protocol 151. J Infect Dis, 170: 189-193.

163. Littler E, Stuart AD, Chee MS. 1992. Human cytomegalovirus UL97 open reading frame encodes a protein that phosphorylates the antiviral nucleoside analogue ganciclovir. Nature, 358: 160-162.
164. Boehme RE. 1984. Phosphorylation of the antiviral precursor 9-(1,3-dihydroxy-2-propoxymethyl)guanine monophosphate by guanylate kinase isozymes. J Biol Chem, 259: 12346-12349.
165. Matthews T, Boehme R. 1988. Antiviral activity and mechanism of action of ganciclovir. Rev Infect Dis, 10 (Suppl. 3): 490-494.
166. Mar EC, Chiou JF, Cheng YC, Huang ES. 1985. Inhibition of cellular DNA polymerasa α and human cytomegalovirus-induced DNA polymerasa by the triphosphates of 9-(2-hydroxyethoxymethyl)guanine and 9-(1,3-dihydroxy-2-propoxymethyl)guanine. J Virol, 53: 776-780.
167. Freitas, V.R., Smee, D.F., Chernow, M., Boehme, R., Matthews, T.R. 1985. Activity of 9-(1,3-dihydroxy-2-propoxymethyl)guanine compared with that of acyclovir against human, monkey, and rodent cytomegaloviruses. Antimicrob Agents Chemother, 28: 240-245.
168. Biron, K.K., Stanat, S.C., Sorrell, J.B., Fyfe, J.A., Keller, P.M., Lambe, C.U., Nelson, D.J. 1985. Metabolic activation of the nucleoside analog 9-{[2-hydroxy-1-(hydroxymethyl) ethoxy]methyl}guanine in human diploid fibroblasts infected with human cytomegalovirus. Proc Natl Acad Sci, 82: 2473-2477.
169. Kuppermann BD, Flores-aguilar M, Quiceno JI, et al. 1993. Combination ganciclovir and foscarnet in the treatment of clinically resistant cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome. Arch Ophthalmol, 111: 1359-1366.
170. Alain S, Honderlick P, Grenet D, et al. 1997. Failure of ganciclovir treatment associated with selection of ganciclovir-resistant cytomegalovirus strain in a lung transplant recipient. Transplantation, 63: 1533-1536.
171. Chou S, Erice A, Jordan MC, et al. 1995. Analysis of the UL97 phosphotransferasa coding sequence in clinical cytomegalovirus isolates and

identification of mutations conferring ganciclovir resistance. J Infect Dis, 171: 576-583.

172. Chou S, Guentzel S, Michels KR, Miner RC, Drew WL. 1995. Frequency of UL97 phosphotransferase mutations related to ganciclovir resistance in clinical cytomegalovirus isolates. J infect Dis, 172: 239-242.
173. Drobyski WR, Knox KK, Carrigan DR, Ash RC. 1991. Foscarnet therapy for ganciclovir-resistant cytomegalovirus in marrow transplantation. Transplantation, 52: 155-157.
174. Smith IL, Shinkai M, Freeman WR, Spector SA. 1996. Polyradiculopathy associated with ganciclovir-resistant cytomegalovirus AIDS patient: phenotypic and genotypic characterization of sequential virus isolates. J Infect Dis, 173: 1481-1484.
175. Smith IL, Cherrington JM, Jiles RE, Fuller MD, Freeman WR, Spector SA. 1997. High-level resistance of cytomegalovirus to ganciclovir is associated with alterations in both the UL97 and DNA polymerasa genes. J Infect Dis, 176: 69-77.
176. Wolf DG, Yaniv I, Honigman A, Kassis I, Schonfeld T, Ashkenazi S. 1998. Early emergence of ganciclovir-resistant human cytomegalovirus strains in children with primary combined immunodeficiency. J Infect Dis, 178: 535-538.
177. Liu W, Kuppermann BD, Martin DF, Wolitz RA, Margolis TP. 1998. Mutations in the cytomegalovirus UL97 gene associated with ganciclovir-resistant retinitis. J Infect Dis, 177: 1176-1181.
178. Jabs DA, Martin BK, Forman MS, et al. 2001. Mutations conferring ganciclovir resistance in a cohort of patiens with acquired immunodeficiency syndrome and cytomegalovirus retinitis. J Infect Dis, 183: 333-337.
179. Limaye AP, Corey L, Koelle DM, Davis CL, Boeckh M. 2000. Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants. Lancet, 356: 645-649.
180. Erice A. 1999. Resistance of human cytomegalovirus to antiviral drugs. Clin Microbiol Rev, 12:286-297.

181. Smith IL, Taskintuna I, Rahhal FM, et al. 1998. Clinical failure of CMV retinitis with intravitreal cidofovir is associated with antiviral resistance. Arch Ophthalmol, 116: 178-185.
182. Wolf DG, Lee DJ, Spector S A. 1995. Detection of human cytomegalovirus mutations associated with ganciclovir resistance in cerebroespinal fluid of AIDS patients with central nervous system disease. Antimicrob Agents Chemother, 39: 2552-2554.
183. Erice A, Gil-Roda C, Pérez JL, et. al. 1997. Antiviral susceptibilities and analysis of UL97 and DNA polymerasa sequences of clinical cytomegalovirus isolates from immunocompromised patients. J Infect Dis, 175: 1087-1092.
184. Erice A, Borrell N, Li W, Miller WJ, Balfour HH. 1998. Ganciclovir susceptibilities and analysis of UL97 region in cytomegalovirus (CMV) isolates from bone marrow recipients with CMV disease after antiviral prophylaxis. J Infect Dis, 178:531-534.
185. Lurain NS, Ammons H, Kapell KS, Yeldandi VV, Garrity ER, O'Keefe JP. 1996. Molecular analysis of human cytomegalovirus strains fromtwo lung transplant recipients with the same donor. Transplantation, 62: 497-502.
186. Wolf DG, Smith IL, Lee DJ, et al. 1995. Mutations in human cytomegalovirus UL97 gene confer clinical resistance to ganciclovir and can be detected directly in patient plasma. J Clin Invest, 95: 257-263.
187. Mendez JC, Sia IG, Tau KR, et al. 1999. Novel mutation inthe CMV UL97 gene associated with resistance to ganciclovir therapy. Transplantation, 67: 755-757.
188. Chou S, Meichsner CL. 2000. A nine-codon deletion mutation in the cytomegalovirus UL97 phosphotransferasa gene confers resistance to ganciclovir. Antimicrob Agents Chemother, 44: 183-185.
189. Sullivan V, Biron KK, Talarico C, et al. 1993. A point mutation in the human cytomegalovirus DNA polymerase gene confers resistance toganciclovir and phosphonylmethoxyalkyl derivatives. Antimicrob Agents Chemother, 37: 19-25.
190. Öberg B. 1989 Antiviral effects of phosphonoformate (PFA, Foscarnet sodium). Pharmac Ther, 40: 213-285.

191. Jacobson MA, Odonnell JJ, Mills J. 1989. Foscarnet treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome. Antimicrob Agents Chemother, 33: 736-741.
192. Ringden O, Lonnquist B, Paulin T, et al. 1986. Pharmacokinetics, safety and preliminary clinical experiences using foscarnet in the treatment of cytomegalovirus infections in bone marrow and renal transplant recipients. J Antimicrob Chemother, 17: 373-387.
193. Palestine AG, Polis MA, De SMD, et al. 1991. A randomized, controlled trial of foscarnet in the treatment of cytomegalovirus retinitis in patients with AIDS. Ann Intern Med, 115: 665-673.
194. Crumpacker CS. 1992. Mechanism of action of foscarnet against viral polymerasas. Am J Med, 92 (Suppl. 2): 3-7.
195. Studies of Ocular Complications of AIDS Research Group in collaboration with AIDS Clinical Trials Group. 1992. Mortality in patients with the acquired immunodeficiency syndrome treated with either foscarnet or ganciclovir for cytomegalovirus retinitis. N Engl J Med, 326: 213-220.
196. Studies of Ocular Complications of AIDS Research Group in collaboration with AIDS Clinical Trials Group. 1996. Combination foscarnet and ganciclovir therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS. The cytomegalovirus retreatment trial. Arch Ophthalmol, 14: 23-33.
197. Coker RJ, Tomlinson D, Horner P, et al. 1991. Treatment of cytomegalovirus retinitis with ganciclovir and foscarnet. Lancet, 338: 574-575.
198. Blanshard C. 1992. Treatment of HIV-related cytomegalovirus disease of the gastrointestinal tract with foscarnet. J AIDS, 5 (Suppl. 1): 25-28.
199. Wilcox CM, Straub RF, Schwartz DZ. 1995. Cytomegalovirus esophagitis in AIDS; a prospective evaluation of clinical response to ganciclovir therapy. Am J Med, 98: 169-176.

200. Domingo P, Puig M, Iranzo A, et al. 1994. Polyradiculopathy due to cytomegalovirus infection; report of a case in which an AIDS patient responded to foscarnet therapy. Clin Infect Dis, 18: 1019-1021.
201. De Gans J, Portegies P, Tiessens G, et al. 1990. Therapy for cytomegalovirus polyradiculomielitis in patients with AIDS: treatment with ganciclovir. AIDS, 4: 421-425.
202. Enting R, DE Gans J, Reiss K, et al. 1992. Ganciclovir/foscarnet for cytomegalovirus meningoencephalitis in AIDS. Lancet, 340: 559-560.
203. Karmochkine M, Molina JM, Scieux C, et al. 1994. Combined therapy with ganciclovir and foscarnet for cytomegalovitus polyradiculomyelitis in patients with AIDS. Am J Med, 97: 196-197.
204. Reusser P, Gambertoglio JG, Lilleby K, et al. 1992. Phase I-II trial of foscarnet for prevention of cytomegalovirus infection in autologous and allogeneic marrow transplant recipients. J Infect Dis, 166: 473-479.
205. Razis E, Cook P, Mittleman A, Ahmed T. 1994. Treatment of ganciclovir resistant cytomegalovirus with foscarnet; a report of two cases occurring after bone marrow transplantation. Leuk Lymphoma, 12: 477-480.
206. Chou S, Marousek G, Guentzel S, et al. 1997. Evolution of mutations conferring multidrug resistance during prophylaxis and therapy for cytomegalovirus disease. J Infect Dis, 176:786-789.
207. Chou S, Marousek G, Parenti DM, et al. 1998. Mutation in region III of the DNA polymerasa gene conferring foscarnet resistance in cytomegalovirus isolates from 3 subjects receiving prolonged antiviral therapy. J Infect Dis, 178:526-530.
208. Visse B, Dumont B, Huraux J, Fillet A. 1998. Single amino acid change in DNA polymerase is associated with foscarnet resistance in a varicella-zoster virus strain recovered from a patient with AIDS. J Infect Dis, 178 (Suppl. 1): 55-57.
209. Sehgal PB, Tamm I. 1980. Antiviral agents:determination of activity. En: Lorian V, ed. Antibiotics in laboratory medicine. Williams & Wilkins, London, p. 573-591.

210. Quantitative assay of virus isolates. 1967. En: Hoskins JM, ed. Virological Procedures. Butterworth & Co, London, p. 169-186.
211. Drew WL, Miner RC, Busch DF, et al. 1991. Prevalence of resistance in patients receiving ganciclovir for serious cytomegalovirus infection. J Infect Dis, 163: 716-719.
212. Baldanti F, Biron KK, Gerna G. 1998. Interpretating human cytomegalovirus antiviral drug susceptibility testing: The role of mixed virus populations. J Infect Dis, 177: 823-824.
213. Drew WL, Miner R, Saleh E. 1993. Antiviral susceptibility testing of cytomegalovirus: criteria for detecting resistance to antivirals. Clin Diagnos Microbiol, 1: 179-185.
214. Parris DS, Harrington JE. 1982. Herpes simplex virus variants resistant to high concentrations of acyclovir exist in clinical isolates. Antimicrob Agents Chemother, 22: 71-77.
215. Nugier F, Colin JN, Aymard M, Langlois M. 1992. Occurrence and characterization of acyclovir-resistant herpes simplex virus isolates: Report on a two-year sensitivity screening survey. J Med Virol, 36: 1-12.
216. Sacks SL, Wanklin RJ, Reece DE, Hicks KA, Tyler KL, Coen DM. 1989. Progressive esophagitis from acyclovir-resistant herpes simplex. Clinical roles for DNA polymerasa mutants and viral heterogeneity?. Ann Intern Med, 111:893-899.
217. Stanat SC, Reardon JE, Erice A, Jordan MC, Drew WL, Biron KK. 1991. Ganciclovir-resistant cytomegalovirus clinical isolates: mode of resistance to ganciclovir. Antimicrob Agents Chemother, 35: 2191-2197.
218. Wolf DG, Yaniv I, Ashkenazi S, Honigman A. 2001. Emergence of multiple human cytomegalovirus ganciclovir-resistant mutants with deletions and substitutions within the UL97 gene in a patient with severe combined immunodeficiency. Antimicrob Agents Chemother, 45: 593-595.

219. Establishing the role of genes within cells. 1992. En: Watson JD, Gilman M, Witkowski J, Zoller M, eds. Recombinant DNA. Scientific American Books, New York, p. 1-11.
220. Harmenberg J, Wahren B, Öberg B. 1980. Influence of cells and virus multiplicity on the inhibition of herpesviruses with acycloguanosina. Intervirology, 14: 239-244.
221. De Clercq, E. 1982. Comparative efficacy of antiherpes drugs in different cell lines. Antimicrob Agents Chemother, 21: 661-663.
222. Swierkosz EM, Hodinka RL. 1999. Antiviral agents and susceptibility tests. En: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, eds. Manual of clinical microbiology. 7ª ed. American Society for Microbiology, ASM Press, Washington, D.C., p. 1624-1639.
223. Hill EL, Ellis MN, Nguyen-Dinh P. 1991. Antiviral and antiparasitic susceptibility testing. En: Balows A, Hausler WJ, Herrmann KL, Isenberg HD, Shadomy HJ et al., eds. Manual of clinical microbiology. 5ª ed. ASM Press, Washington, D.C., p. 1184-1191.
224. Clarke LM. 1992. Viruses, rickettsiae, Chlamydiae, and mycoplasmas. En: Isenberg HD, ed. Clinical microbiology procedures handbook. American Society for Microbiology, Washington, D.C., Section 8.
225. Chatis, P.A., Crumpacker, C.S. 1992. Resistance of Herpesviruses to antiviral drugs. Antimicrob Agents Chemother, 36: 1589-1595.
226. Englund JA, Zimmerman ME; Swierkosz, EM, et al. 1990. Herpes simplex virus resistant to acyclovir. A study in a tertiary care center. Ann Intern Med, 112:416-422.
227. Erice A, Chou S, Biron KK, Stanat SC, Balfour HH, Jordan MC: 1989. Progressive disease due to ganciclovir-resistant cytomegalovirus in immunocompromised patients. N Engl J Med, 320: 289-293.
228. Jacobson MA, Berger TG, Fikrig S, et al. 1990. Acyclovir-resistant varicella zoster virus infection after chronic oral acyclovir therapy in patients with the acquired immunodeficiency syndrome (AIDS). Ann Intern Med, 112: 187-191.

229. Pahwa S, Biron K, Lim W, et al. 1988. Continuous varicella-zoster infection associated with acyclovir resistance in a child with AIDS. JAMA, 260: 2879-2882.
230. Safrin S, Crumpacker C, Chatis, P, et al. 1991. A controlled trial comparing foscarnet with vidarabine for acyclovir-resistant mucocutaneous herpes simplex in the acquired immunodeficiency syndrome. N Engl J Med, 325:551-555.
231. Sibrack CD, Gutman LT, Wilfert CM, et al. 1982. Pathogenicity of acyclovir-resistant herpes simplex virus type 1 from immunodeficient child. J Infect Dis, 146:673-682.
232. Christophers J, Sutton RNP, Noble RV, Anderson H. 1986. Clinical resistance to acyclovir of herpes simplex virus infections in immunocompromised patients. J Antimicrob Chemother, 18 (Suppl. B): 121-125.
233. Gateley A, Gander RM, Johnson PC, Kit S, Otsuka H, Kohl S. 1990. Herpes simplex virus type 2 meningoencephalitis resistant to acyclovir in a patient with AIDS. J Infect Dis, 161: 711-715.
234. Schinazi RF, del Bene V, Scott RT Dudley-Thorpe JB. 1986. Characterization of acyclovir-resistant and –sensitive herpes simplex viruses isolated from a patient with acquired immune deficiency. J Antimicrob Chemother, 18 (Suppl. B): 127-134.
235. Crumpacker CS, Schnipper LE, Marlowe SI, Kowalsky PN, Hershey BJ, Levin MJ. 1982. Resistance to antiviral drugs of herpes simplex virus isolated from a patient treated with acyclovir. N Engl J Med, 306: 343-346.
236. Christophers J, Sutton RNP. 1987. Characterization of acyclovir-resistant and –sensitive clinical herpes simplex virus isolates from an immunocompromised patient. J Antimicrob Chemother, 20: 389-398.
237. Rosen HR, Benner KG, Flora KD et al. 1997. Development of ganciclovir resistance during treatment of primary cytomegalovirus infection after liver transplantation. Transplantation, 63: 476-478.
238. Slavin MA, Bindra RR, Gleaves CA, Pettinger MB, Bowden RA. 1993. Ganciclovir sensitivity of cytomegalovirus at diagnosis and during treatment of

cytomegalovirus Pneumonia in marrow transplant recipients. Antimicrob Agents Chemother, 37: 1360-1363.

239. Baldanti F, Simoncini L, Talarico CL, Sarasini A, Biron KK, Gerna G. 1998. Emergence of a ganciclovir-resistant human cytomegalovirus strain with a new UL97 mutation in an AIDS patient. AIDS, 12: 816-818.
240. Christophers J, Clayton J, Craske J, et al. 1998. Survey of resistanceof herpes simplex virus to acyclovir in northwest England. Antimicrob Agents Chemother, 42: 868-872.
241. Darby G, Field HJ. 1981. Altered substrate specificity of herpes simplex virus thymidine kinase confers acyclovir-resistance. Nature, 289: 81-83.
242. Ellis MN, Keller PM, Fyfe JA, et al. 1987. Clinical isolate of herpes simplex virus type 2 that induces a thymidine kinase with altered substrate specificity. Antimicrob Agents Chemother, 31: 1117- 1125.
243. Kit S, Sheppard M, Ichimura H, et al. 1987. Nucleotide sequence changes in thymidine kinase gene of herpes simplex virus type 2 clones from an isolate of a patient treated with acyclovir. Antimicrob Agents Chemother, 31: 1483-1490.
244. Parker AC, Craig JIO, Collins P, Oliver N, Smith I. 1987. Acyclovir-resistant herpes simplex virus infection due to altered DNA polymerasa. Lancet, 2:1461.
245. Kost RG, Hill EL, Tigges M, Straus SE. 1993. Brief report: recurrent acyclovir-resistant genital herpes in an immunocompetent patient. N Engl J Med, 329: 1777-1782.
246. Hwang CB, Horsburgh B, Pelosi E, Roberts S, Digard P, Coen DM. 1994. A net +1 frameshift permits synthesis of thymidine kinase from a drug-resistant herpes simplex virus mutant. Proc Natl Acad Sci, 91:5461-5465.
247. Swetter SM, Hill EL, Kern ER, et al. 1998. Chronic vulvar ulceration in an immunocompetent woman due to acyclovir-resistant, thymidine kinase-deficient herpes simplex virus. J Infect Dis, 177: 543-550.
248. Lee NY, Tang YW, Espy MJ et al. 1999. Role of genotypic analysis of the thymidine kinase gene of herpes simplex virus for determination of neurovirulence and resistance to acyclovir. J Clin Microbiol, 37: 3171-3174.

249. Gibbs JS, Chiou HC, Bastow KF, Cheng Y, Coen DM. 1988. Identification of amino acids in herpes simplex virus DNA polymerasa involved in substrate and drug recognition. Proc Natl Acad Sci, 85: 6672-6676.
250. Coen DM. 1994. Acyclovir-resistant, pathogenic herpesviruses. Trends Microbiol, 2: 481-484.
251. Field HJ, Darby G. 1980. Pathogenicity in mice of strains of herpes simplex virus which are resistant to acyclovir *in vitro* and *in vivo.* Antimicrob Agents Chemother, 17: 209-216.
252. Tenser RB, Jones JC, Ressel SJ. 1985. Acute and latent infection by thymidine kinase mutants of herpes simplex virus type 2. J Infect Dis, 151: 548-550.
253. Sibrack CD, McLaren C, Barry DW. 1982. Disease and latency characteristics of clinical herpes simplex virus isolates after acyclovir therapy. Amer J Med, 73: 372-375.
254. Coen DM, Kosz-Vnenchak M, Jacobson JG, et al. 1989. Thymidine kinase-negative herpes simplex virus mutants establish latency in mouse trigeminal ganglia but do not reactivate. Proc Natl Acad Sci, 86: 4736-4740.
255. Hill EL, Hunter GA, Ellis MN. 1991. *In vitro* and *in vivo* characterization of herpes simplex virus clinical isolates recovered from patients infected with human immunodeficiency virus. Antimicrob Agents Chemother, 35: 2322-2328.
256. Dekker C, Ellis MN, McLaren C, Hunter G, Rogers J, Barry DW. 1983. Virus resistance in clinical practice. J Antimicrob Chemother, 12, Suppl. B: 137-152.
257. Morfin F, Thouvenot D, Aymard M, Souillet G. 2000. Reactivation of acyclovir-resistant thymidine kinase-deficient herpes simplex virus harbouring single base insertion within a 7 Gs homopolymer repeat of the thymidine kinase gene. J Med Virol, 62: 247-250.
258. Sasadeusz JJ, Sacks SL. 1996. Spontaneous reactivation of thymidine kinase-deficient, acyclovir-resistant type 2 herpes simplex virus: masked heterogeneity or reversion?. J Infect Dis, 174: 476-482.

259. Sarisky RT, Nguyen TT, Duffy KE, Wittrock RJ, Leary JJ. 2000. Difference in incidence of spontaneous mutations between herpes simplex virus type 1 and 2. Antimicrob Agents Chemother, 44: 1524-1529.
260. Erlich KS, Mills J, Chatis P, et al. 1989. Acyclovir-resistant herpes simplex virus infections in patients with the acquired immunodeficiency syndrome. N Engl J Med, 320: 293-296.
261. Ljungman P, Ellis MN, Hackman RC, Shepp DH, Meyers JD. 1990. Acyclovir-resistant herpes simplex virus causing pneumonia after marrow transplantation. J Infect Dis, 162: 244-248.
262. Birch CJ, Tachedjian G, Doherty RR, Hayes K, Gust ID. 1990. Altered sensitivity to antiviral drugs of herpes simplex virus isolates from a patient with the acquired immunodeficiency syndrome. J Infect Dis, 162: 731-734.
263. Safrin S. 1992. Treatment of acyclovir-resistant herpes simplex virus infections in patients with AIDS. J AIDS, 5 (Suppl. 1): 29-32.
264. Ambinder RF, Burns WH, Lietman PS, Saral R. 1984. Prophylaxis: a strategy to minimise antiviral resistance. Lancet, 1: 1154-1155.
265. McLaren C, Lawrence C, Dekker C, Barry DW. 1983. *In vitro* sensitivity to acyclovir in genital herpes simplex viruses from acyclovir-treated patients. J Infect Dis, 148: 868-875.
266. Nusinoff Lehrman S, Hill EL, Rooney JF, Ellis MN, Barry DW, Straus SE. 1986. Extended acyclovir therapy for herpes genitalis: changes in virus sensitivity and strain variation. J Antimicrob Chemother, 18, Suppl. B: 85-94.
267. Nusinoff Lehrman S, Douglas JM, Corey L, Barry DW. 1986. Recurrent genital herpes and suppressive oral acyclovir therapy. Relation between clinical outcome and *in vitro* drug sensitivity. Ann Intern Med, 104: 786-790.
268. Fife KH, Crumpacker CS, Mertz GJ, Hill EL, Boone GS, and the Acyclovir Study Group. 1994. Recurrence and resistance patterns of herpes simplex virus following cessation of ≥ 6 years of chronic suppression with acyclovir. J Infect Dis, 169: 1338-1341.

269. Hasegawa T, Kawana T, Okuda T, Horii M, Tsukada T, Shiraki K. 2001. Susceptibility to acyclovir of herpes simplex virus isolates obtained between 1977 and 1996 in Japan. J Med Virol, 63: 57-63.
270. Biron KK, Fyfe JA, Stanat SC, et al. 1986. A human cytomegalovirus mutant resistant to the nucleoside analog 9-{[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl} guanine (BW B759U) induces reduced levels of BW B759U triphosphate. Proc Natl Acad Sci, 83: 8769-8773.
271. Sullivan V, Talarico CL, Stanat SC, Davis M, Coen DM, Biron KK. 1992. A protein kinasa homologue controls phosphorylation of ganciclovir in human cytomegalovirus-infected cells. Nature, 358: 162-164.
272. Erice A, Jordan MC, Chace BA, Fletcher C, Chinnock BJ, Balfour HH. 1987. Ganciclovir treatment of cytomegalovirus disaease in transplant recipients and other immunocompromised hosts. JAMA, 257: 3082-3087.
273. Baldanti F, Underwood MR, Talarico CL, et al. 1998. The Cys607→Tyr change in the UL97 phosphotransferase confers ganciclovir resistance to two human cytomegalovirus strains recovered from two immunocompromised patients. Antimicrob Agents Chemother, 42: 444-446.
274. Hanson MN, Preheim LC, Chou S, Talarico CL, Biron KK, Erice A. 1995. Novel mutation in the UL97 gene of a clinical cytomegalovirus strain conferring resistance to ganciclovir. Antimicrob Agents Chemother, 39: 1204-1205.
275. Snoeck R, Gérard M, Sadzot-Delvaux, et. Al. 1993. Meningoradiculoneuritis due to acyclovir-resistant varicella-zoster virus in a patient with AIDS [carta]. J Infect Dis, 168: 1330-1331.
276. Fillet A, Visse B, Caumes E, Dumont B, Gentilini M, Huraux J. 1995. Foscarnet-resistant multidermatomal zoster in a patient with AIDS. Clin Infect Dis, 21: 1348-1349.
277. Rawls WE. 1979. Herpes simplex virus types 1 and 2 and herpesvirus simiae. En: Lennette EH, Schmidt, NJ, eds. Diagnostic proceduresfor viral, rickettsial and chlamydial infections. American public health association, Washington, D.C., p. 309-373.

278. Whitaker A. 1972. Tissue and cell culture of higher animals. En: Whitaker A., ed. Tissue and cell culture. Baillière Tindall, p. 25-65.
279. Reynolds DW, Stagno S, Alford CA. 1979. Laboratory diagnosis of cytomegalovirus infections. En: Lennette EH, Schmidt NJ, eds. Diagnostic procedures for viral, rickettsial and chlamydial infections. American public health association, Washington, D.C., p. 399-439.
280. Weller TH. 1979. Varicella and herpes zoster. En: Lennette EH, Schmidt NJ, eds. Diagnostic proceduresfor viral, rickettsial and chlamydial infections. American public health association, Washington, D.C., p. 375-398.
281. Propagation and titration of virus. 1973. En: Rovozzo GC, Burke CN, eds. A manual of basic virological techniques. Prentice-Hall, Inc., Englewood Cliffs, New Jersey, p. 64-93.
282. Quantitative methods. 1973. En: Cunningham CH, ed. A laboratory guide in virology. Burgess publishing company, Minnesota, p. 79-92.
283. Kärber G. 1931. Beitrag zur kollektiven Behandlung pharmakologischer Reihenversuche. Arch Exper Pathol Pharmakol, 162: 480-483.
284. Virological applications of tissue culture. 1970. En: Cumming H, ed. Virology-Tissue culture. Butterworths, London, p. 47-61.
285. McLaren C, Ellis MN, Hunter GA. 1983. A colorimetric assay for measurement of the sensitivity of herpes simplex viruses to antiviral agents. Antiviral Res, 3: 223-234.
286. Hendrickson DA, Krenz MM. 1991. Reagents and stains. En: Balows A, Hausler WJ, Herrmann KL, Isenberg HD, Shadomy HJ, eds. Manual of clinical microbiology. ASM, Washington, D.C., p. 1289-1314.
287. Assay of antibodies by neutralization. 1967. En: Hoskins JM, ed. Virological Procedures. Butterworth & Co., London, p. 236-240.
288. Biron KK; Elion GB. 1980. In vitro susceptibility of varicella-zoster virus to acyclovir. Antimicrob Agents Chemother, 18: 443-447.

289. Machida H, Kuninaka A, Yoshino H. 1982. Inhibitory effects of antiherpesviral thymidine analogs against varicella-zoster virus. Antimicrob Agents Chemother, 21: 358-361.
290. Swierskosz EM, Scholl DR, Brown JL, Jollick JD, Gleaves CA. 1987. Improved DNA hybridization method for detection of acyclovir-resistant herpes simplex virus.Antimicrob Agents Chemother, 31: 1465-1469.
291. Barry DW, Nusinoff-Lehrman S, Ellis MN. 1986. Clinical and laboratory experience with acyclovir-resistant herpes viruses. J Antimicrob Chemother, 18 (Suppl. B): 75-84.
292. Öberg B, Johansson NG. 1984. The relative merits and drawbacks of new nucleoside analogues with clinical potential. J Antimicrob Chemother, 14, Suppl. A: 5-26.
293. Harmenberg J. 1983. Intracellular pools of thymidine reduce the antiviral action of acyclovir. Intervirology, 20: 48-51.
294. Ho M, Enders JF. 1959. An inhibitor of viral activity appearing in infected cell cultures. Proc Natl Acad Sci U.S.A., 45:385-389.
295. De Clercq E, Descamps J, Verhelst G et al. 1980. Comparative efficacy of antiherpes drugs against different strains of herpes simplex virus. J Infect Dis, 141: 563-574.
296. McLaren C, Sibrack CD, Barry DW. 1982. Spectrum of sensitivity to acuclovir of herpes simplex virus clinical isolates. Am J Med, 73: 376-379.
297. Kruppenbacher JP, Kläss R, Eggers HJ. 1994. A rapid and reliable assay for testing acyclovir sensitivity of clinical herpes simplex virus isolates independent of virus dose and reading time. Antiviral Res, 23: 11-22.
298. Salmerón F, Hernaez R. 1986. *In vitro* sensitivity of herpes simplex virus types 1 and 2 isolates against 9-ß-D-arabino-furanosyladenine, 9-((2-hydroxy-1-(hydroxymethyl) ethoxy) methyl)guanine and 9-(2-hydroxyethoxymethyl) guanine. Microbiología 2: 11-16.

299. Salmerón F, Hernáez R, Rodríguez C. 1989. *In vitro* sensitivity of clinical isolates and drug-resistant mutants of herpes simplex virus against seven antiviral drugs. J Chemother, (Suppl. 4): 1110-1112.
300. Otegui M, Rabella Labeaga R, Mercader M, Margall N, Prats G. 1997. Valores de sensibilidad *in vitro* al aciclovir y al foscarnet de las cepas de virus herpes simple aisladas de pacientes inmunodeprimidos. Rev Esp Quimioterapia, 10:43-48.
301. Rodriguez MC, Hernáez R, Salmerón, F. 1989. Sensibilidad a varios antivíricos de cuatro cepas de virus herpes simplex de los tipos 1 y 2 resistentes al 2'fluor-2'desoxi-5-metil-arabinofuranosiluracilo (FMAU). Rev Esp Microbiol Clin, 4: 341-346.
302. Andrei G, Snoeck R, Goubau P, Desmyter J, De Clerq E. 1992. Comparative activity of various compounds against clinical strains of herpes simplex virus. Eur J Clin Microbiol Infect Dis, 11: 143-151.
303. Collazo MV, Pérez P, Salmerón F. 1986. Sensibilidad de 56 aislados de virus herpes simplex de los tipos 1 y 2 en un ensayo *in vitro* frente a fosfonoformiato sódico en células Hep-2. Infectologika, 3: 7-13.
304. Crumpacker CS, Schnipper LE, Zaia JA, Levin MJ. 1979. Growth inhibition by acycloguanosine of herpes viruses isolated from human infections. Antimicrob Agents Chemother, 15: 642-645.
305. Collins P. 1983. The spectrum of antiviral activities of acyclovir *in vitro* and *in vivo*. J Antimicrob Chemother, 12 (Suppl. B): 19-27.
306. Barry DW, Nusinoff-Lehrman S, Ellis MN, Biron KK, Furman PA. 1985. Virus resistance: Clinical experience. Scand J Infect Dis, (Suppl. 47): 155-164.
307. Swierskosz EM, Biron KK. 1995. Antiviral agents and susceptibility testing. En: Murray PR, et al., eds. Manual of clinical microbiology. 6ª ed. ASM Press, Washington D.C., p. 1415-1423.
308. Collins P, Ellis MN. 1993. Sensitivity monitoring of clinical isolates of herpes simplex virus to acyclovir. J Med Virol, Suppl. 1: 58-66.

309. Langlois M, Allard JP, Nugier F, Aymard M. 1986. A rapid and automated colorimetric assay for evaluating the sensitivity of herpes simplex strains to antiviral drugs. J Biol Standarization, 14: 201-211.
310. Corey L, Spear PG. 1986. Infections with herpes simplex viruses. N Engl J Med, 314: 686-691.
311. Sullivan, V. And Coen, D.M. 1991. Isolation of foscarnet-resistant human cytomegalovirus patterns of resistance and sensitivity to other antiviral drugs. J Infect Dis, 164: 781-784.
312. Rush, J. And Mills, J. 1987. Effect of combinations of difluoromethylornithine (DFMO) and 9[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG) on human cytomegalovirus. J Med Virol 21: 269-276.
313. Tatarowicz, W.A., Lurain, N.S., Thompson, K.D. 1992. A ganciclovir-resistant clinical isolate of human cytomegalovirus exhibiting cross-resistance to other DNA polymerasa inhibitors. J Infect Dis, 166: 904-907.
314. Pepin, J.M., Simon, F., Dussault, A., Collin, G., Dazza, M.C., Brun-Vezinet, F. Rapid determination of human cytomegalovirus susceptibility to ganciclovir directly from clinical specimen primocultures. J Clin Microbiol 1992; 30: 2917-2920.
315. Manischewitz, J.F., Quinnan, G.V.Jr., Clifford Lane, H., Wittek, A.E. Synergistic effect of ganciclovir and foscarnet on cytomegalovirus replication *in vitro.* Antimicrob Agents Chemother 1990; 34: 373-375.
316. Field, A.K., Davies, M.E., DeWitt, C., Perry, H.C., Liou, R., Germershausen, J., Karkas, J.D., Ashton, W.T., Johnston, D.B.R., Tolman, R.L. 1983. 9-{[2-hydroxy-1-(hydroxymethyl) ethoxy]methyl}guanine: A selective inhibitor of herpes group virus replication. Proc Natl Acad Sci, 80: 4139-4143.
317. Tocci, M.J., Livelli, T.J., Perry, H.C., Crumpacker, C.S., Kirk, A. Effects of the nucleoside analog 2'-nor-2'-deoxyguanosine on human cytomegalovirus replication. Antimicrob Agents Chemother 1984; 25: 247-252.

318. Smee, D.F., Martin, J.C., Verheyden, J.P.H., Matthews, T.R. 1983. Anti-herpesvirus activity of the acyclic nucleoside 9-(1,3-dihydroxy-2-propoxymethyl)guanine. Antimicrob Agents Chemother, 23: 676-682.
319. Plotkin, S.A., Drew, W.L., Felsenstein, D., Hirsch, M.S. 1985. Sensitivity of clinical isolates of human cytomegalovirus to 9-(1,3-dihydroxy-2-propoxymethyl)guanine. J Infect Dis, 152: 833-834.
320. Snoeck, R., Andrei, G., Schols, D., Balzarini, J., De Clerq, E. 1992. Activity of different antiviral drug combinations against human cytomegalovirus replication *in vitro*. Eur J Clin Microbiol Infect Dis, 11: 1144-1155.
321. Snoeck, R., Andrei, G., De Clerq, E. 1996. Patterns of resistance and sensitivity to antiviral compounds of drugs-resistant strains of human cytomegalovirus selected *in vitro*. Eur J Clin Microbiol Infect Dis, 15: 574-579.
322. Cheng, Y.C., Huang, E.S., Lin, J.C., Mar, E.C., Pagano, J.S., Dutschman, G.E., Grill, S.P. 1983. Unique spectrum of activity of 9-[(1,3-dihydroxy-2-propoxy)methyl]-guanine against herpesviruses *in vitro* and its mode of action against herpes simplex virus type 1. Proc Natl Acad Sci, 80: 2767-2770.
323. Mar, E.C., Cheng, Y.C., Huang, E.S. 1983. Effect of 9-(1,3-dihydroxy-2-propoxymethyl)guanine on human cytomegalovirus replication *in vitro.* Antimicrob Agents Chemother, 24: 518-521.
324. Gerna, G., Sarasini, A., Percivalle, E., Zavattoni, M., Baldanti, F., Revello, G. 1995. Rapid screening for resistance to ganciclovir and foscarnet of primary isolates of human cytomegalovirus from culture-positive blood samples.J Clin Microbiol, 33: 738-741.
325. Shepp, D.H., Dandliker, P.S., De Miranda, P., Burnette, T.C., Cederberg, D.M., Kirk, L.E., Meyers, J.D. 1985. Activity of 9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine in the treatment of cytomegalovirus pneumonia. Ann Intern Med, 103: 368-373.
326. Calicó, I., Balada, E., Cortés Borra, A., Mercader, E. 1996. A simplified technique for determining the sensitivity of cytomegalovirus strains to ganciclovir. J Virol Methods, 60: 59-64.

327. Dunn, J.P., MacCumber, M.W., Forman, M.S., Charache, P., Apuzzo, L., Jabs, D.A. 1995. Viral sensitivity testing in patients with cytomegalovirus retinitis clinically resistant to foscarnet or ganciclovir. Am J Ophthalmol, 119; 587-596.
328. Boivin G, Chou S, Quirk MR, Erice A, Colin Jordan M. 1996. Detection of ganciclovir resistance mutations and quantitation of cytomegalovirus (CMV) DNA in leukocytes of patients with fatal dissemonated CMV disease. J Infect Dis, 173: 523-528.
329. Jabs, D.A., Dunn, J.P., Enger, C., Forman, M., Bressler, N., Charache, P., for the CMV retinitis and viral resistance study group. 1996. Cytomegalovirus retinitis and viral resistance. Prevalence of resistance at diagnosis, 1994. Arch Ophthalmol, 114: 809-814.
330. Studies of Ocular Complications of AIDS (SOCA) in collaboration with the AIDS Clinical Trial Group. 1997. Cytomegalovirus (CMV) culture results, drug resistance, and clinical outcome in patients with AIDS and CMV retinitis treated with foscarnet or ganciclovir. J Infect Dis, 176: 50-58.
331. Gilbert C, Hanfield J, Toma E, et al. 1998. Emergence and prevalence of cytomegalovirus UL97 mutations associated with ganciclovir resistance in AIDS patients. AIDS, 12: 125-129.
332. Landry, M.L., Stanat, S., Biron, K., Brambilla, D., Britt W., Jokela, J. et al. 2000. A standarized plaque reduction assay for determination of drug susceptibilities of cytomegalovirus clinical isolates. Antimicrob Agents Chemother, 44:688-692.
333. Swierkosz, E.M. Antiviral susceptibility testing: coming of age. ASM News 1992; 58: 83-87.
334. Shiraki K, Ochiai H, Namazue J, et al. 1992. Comparison of antiviral assay methods using cell-free and cell-associated varicella-zoster virus. Antiviral Res, 18: 209-214.
335. Cole NL, Balfour HH. 1986. Varicella-zóster virus does not become more resistant to acyclovir during therapy. J Infect Dis, 153: 605-608.

336. Machida H. 1986. Comparison of susceptibilities of varicella-zoster virus and herpes simplex viruses to nucleoside analogs. Antimicrob Agents Chemother, 29: 524-526.
337. Sakuma T, Saijo M, Suzutani T, et al. 1991. Antiviral activity of oxetanocins against varicella-zoster virus. Antimicrob Agents Chemother, 35: 1512-1514.
338. Andrei G, Snoeck R, Liesnard C, et al. 1995. Comparative activity of selected antiviral compounds against clinical isolates of varicella-zoster virus. Eur J Clin Microbiol Infect Dis, 14: 318-328.
339. Wunderli W, Miner R, Wintsch J, Von Gunten S, Hirsch HH, Hirschel B. 1996. Outer retinal necrosis due to a strain of varicella-zoster virus resistant to acyclovir, ganciclovir, and sorivudine. Clin Infect Dis, 22: 864-865.