Resistance of Herpes Simplex Virus to Acyclovir

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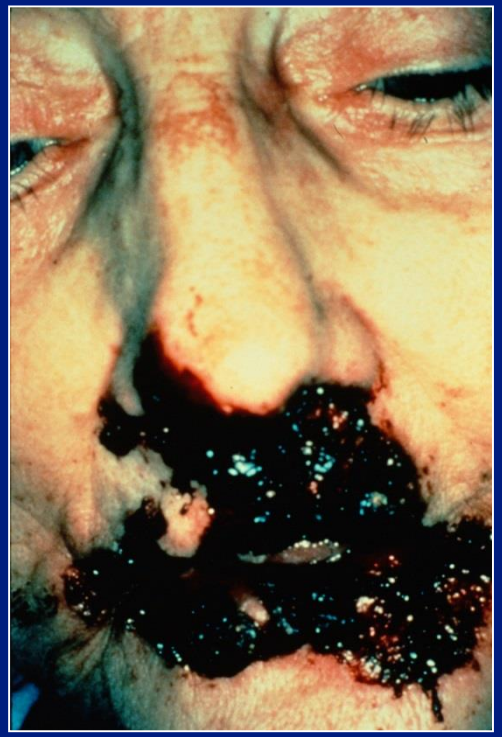
Prevalence of Acyclovir-Resistant HSV Infections

- In immunocompetent indivuals:
  - Varies between 0.1% to 0.7%
  - As high as 6.4% in patients with herpetic keratitis
- In immunocompromised patients:
  - Varies between 3.5% to 14.0%
  - As high as 36.0% in hematopoietic stem cell transplant recipients

Clinical Presentation of Acyclovir-Resistant HSV Infections

- In AIDS patients:
  - Extensive/prolonged mucocutaneous lesions
  - Usually not associated with visceral and CNS infections
- In other immunocompromised subjects:
  - Persistent and/or disseminated diseases

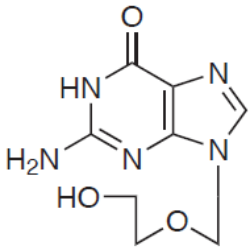


When to Suspect Acyclovir-Resistant HSV Infections

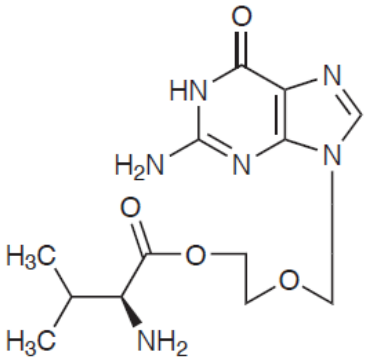
- Persistence of active lesions for >7-10 days after initiation of ACV, VACV or FCV therapy
- No appreciable decrease in size
- Atypical appearance
- Emergence of satellite lesions

From Piret and Boivin (2016) *Curr. Opin. Infect. Dis*. 29:654.

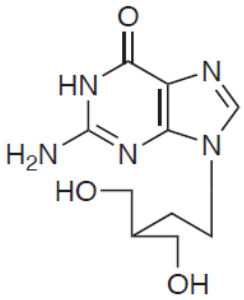
Antiviral Agents for the Prevention and Treatment of Herpetic Infections



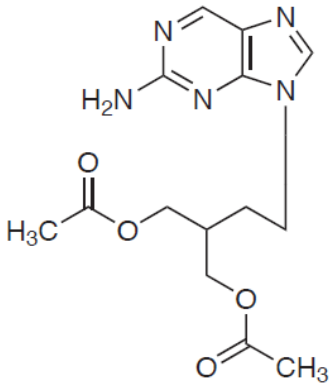
Acyclovir
(ACV)



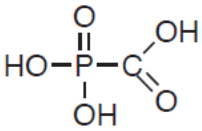
Valacyclovir
(VACV)



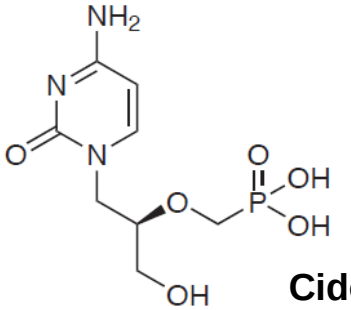
Penciclovir
(PCV)



Famciclovir
(FCV)

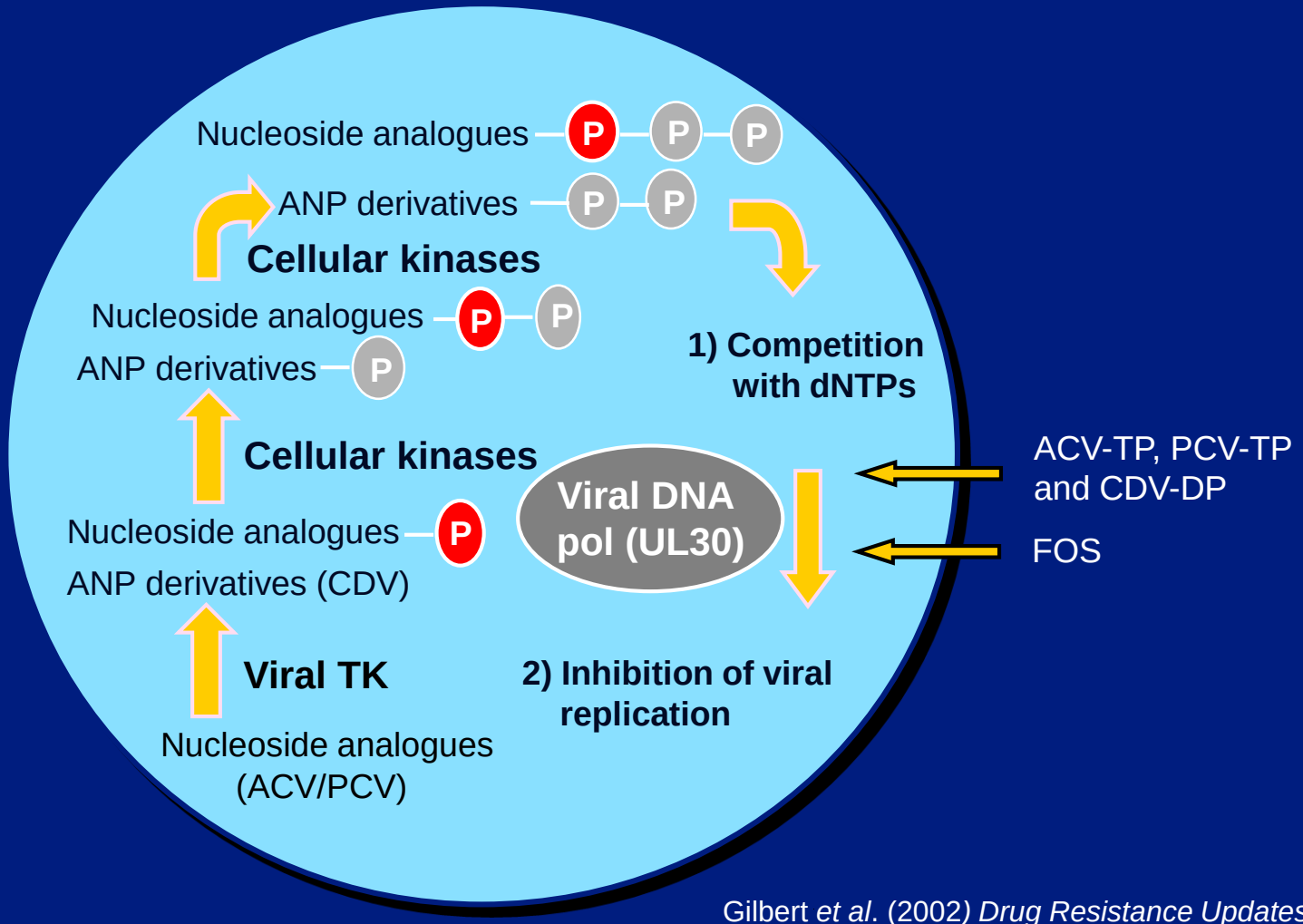


Foscarnet
(FOS)



Cidofovir
(CDV)

Mechanisms of Action of Anti-HSV Drugs



Gilbert *et al*. (2002) *Drug Resistance Updates*. 5:88.

Plaque Reduction Assay (PRA)

Vero cells are infected with HSV (40 PFU/well)

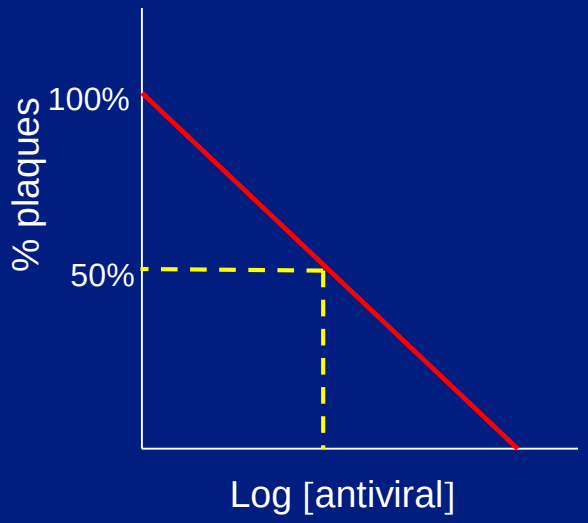
↓ 37°C (CO_2) / 1h30

Increasing conc. (serial dilutions) of ACV are added

↓ 37°C (CO_2) / 2-3 days

Fixation and staining of cells
Plaque counting

↓



50% effective concentration (EC_{50}) = antiviral concentration that reduces the number of plaques by 50% compared to control

ACV resistance: EC_{50} ≥2 µg/mL or 3- to 5-times that of a wild-type reference isolate

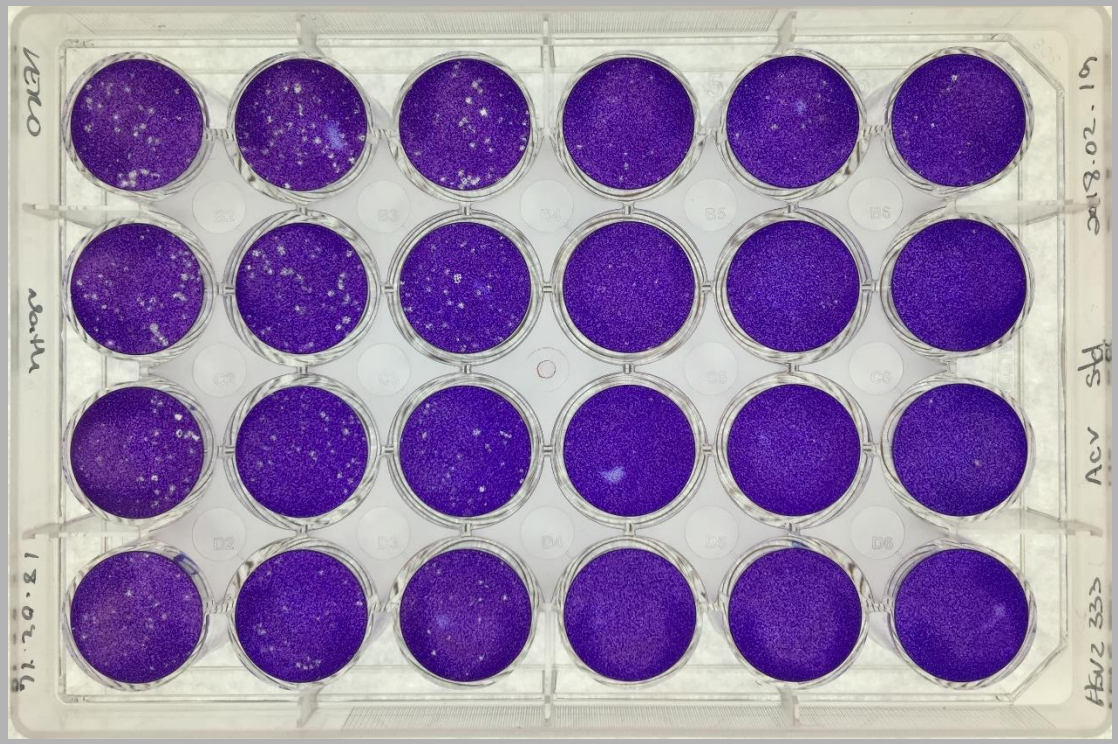
Typical Plaque Reduction Assay with HSV on Vero Cells

No drug

0.25 µg/mL

0.50 µg/mL

1 µg/mL



2 µg/mL

4 µg/mL

8 µg/mL

16 µg/mL

EC_{50} ACV against HSV-2 strain 333 = 1.08 µg/mL

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Mechanisms of HSV-1 and -2 Resistance to Antiviral Agents

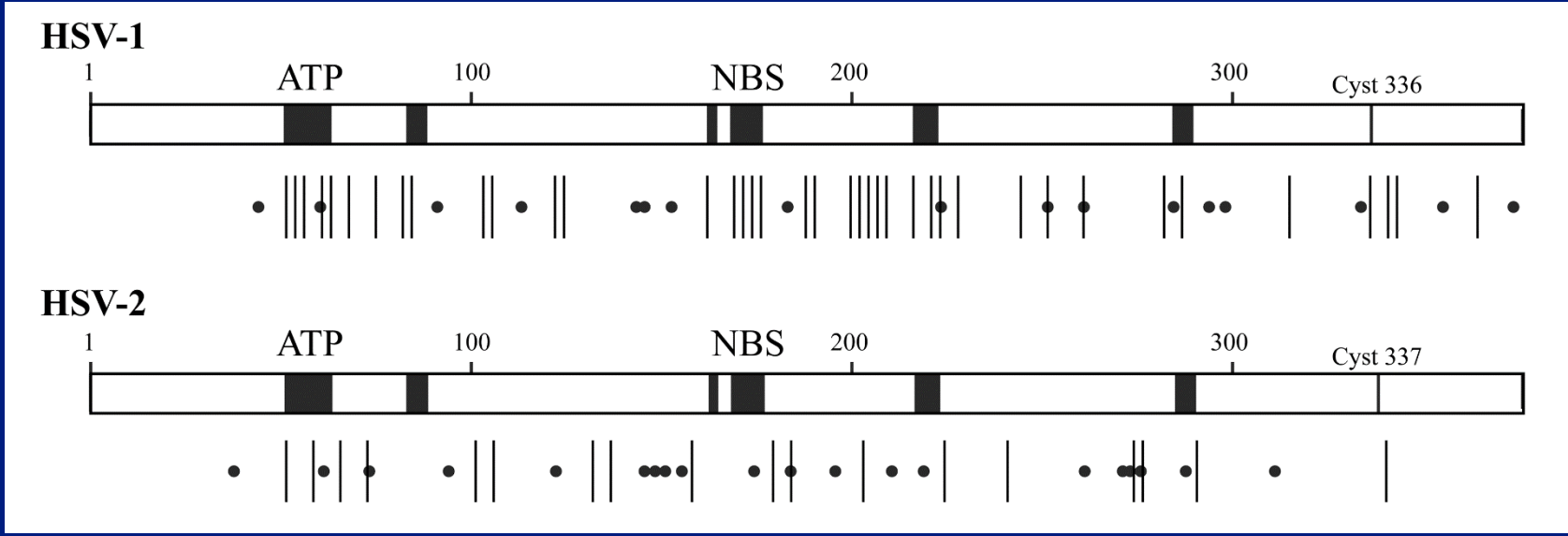
- Resistance to ACV:
  - 95% of cases: Mutations in the viral thymidine kinase (TK)
  - 5% of cases: Mutations in the viral DNA polymerase (pol)

- In the viral TK (*UL23* gene):
  - 50% add./del. of nucleotides
  - 50% amino acid changes
  - Resistance to nucleoside analogues only

- In the viral DNA pol (*UL30* gene):
  - Amino acid changes
  - Possibility of cross-resistance between two or all antiviral agents

Gaudreau *et al.* (1998) *J. Infect. Dis*. 178:297.

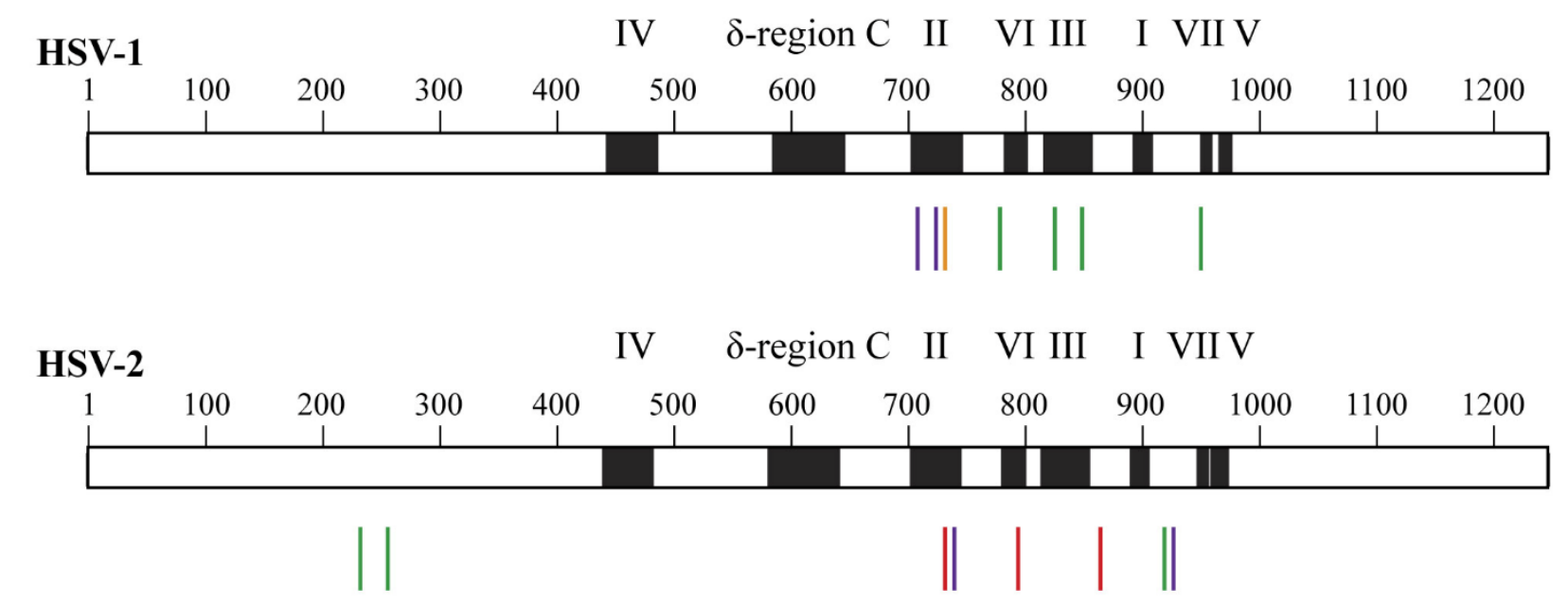
Mutations in *UL23* (TK) Genes of HSV-1 and -2 Conferring Resistance to Acyclovir



ATP, ATP-binding site; NBS, nucleotide-binding site; Cyst, cysteine.
Bars and dots represent amino acid changes and add./del. of nucleotides, respectively.

Adapted from Piret and Boivin (2014) *Rev. Med. Virol.* 24:186.

Mutations in *UL30* (DNA pol) Genes of HSV-1 and -2 Conferring Resistance to Antiviral Agents



Conserved regions IV, δ-region C, II, VI, III, I, VII and V are shown.

ACV^R | FOS^R | ACV^R/FOS^R | ACV^R/FOS^R/CDV^R

Adapted from Piret and Boivin (2014) *Rev. Med. Virol.* 24:186.

Management of Acyclovir-Resistant HSV Infections

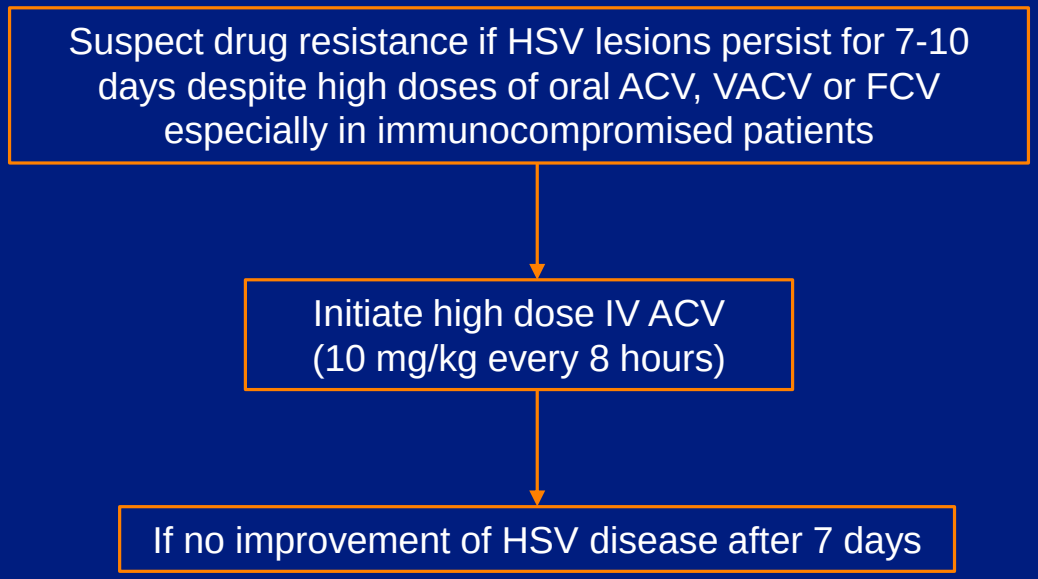
- IV FOS (40 mg/kg every 8 hours)
- Continuous infusion of high-dose ACV (1.5 to 2.0 mg/kg per hour)
- IV CDV (5 mg/kg once a week for 3-4 weeks)
- Topical formulations of FOS and CDV (not commercially available)
- Topical formulation of 5% imiquimod, an immunomodulatory drug
- Topical solution of 1% TFT (ophthalmic herpetic infections)

New Anti-Herpetic Drugs in Clinical Phases of Investigation

- Brincidofovir (CMX001)- Chimerix
  - Lipid ester prodrug of CDV
  - Avoid dose-limiting toxicity of CDV (future uncertain)
- Pritelivir (AIC316)- AiCuris
  - Helicase-primase inhibitor
  - Reduces the rate of genital HSV-2 shedding and days with lesions in a phase II trial (current trial in IC patients)
- Amenamevir (ASP2151)- Maruho
  - Helicase-primase inhibitor
  - Phase III clinical trial completed (unpublished)

Hostetler (2010) *Viruses*. 2:2213; Wald *et al.* (2014) *New Engl. J. Med*. 370:201; Chono *et al.* (2010) *J. Antimicrob. Chemother.* 65:1733.

Proposed Algorithm for the Management of Drug-Resistant HSV Infections (1/2)



High dose oral
ACV = 800 mg 5 times a day
VACV = 1000 mg TID
FCV = 500 mg TID

Adapted from Piret and Boivin (2016) *Curr. Opin. Infect. Dis*. 29:654.

Proposed Algorithm for the Management of Drug-Resistant HSV Infections (2/2)