HIV İLİŞKİLİ SORUNLU VİRAL ENFEKSİYONLARIN YÖNETİMİ

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DİCLE ÜNİVERİSİTESİ
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Eur Respir J 2012; 39: 730–745
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REVIEW

Pulmonary infections in HIV-infected patients: an update in the 21st century

N. Benito*, A. Moreno#, J.M. Miro# and A. Torres¶+

Etyolojik ajanlar	İnsidans (Pulmoner infiltrasyon)
Bakteriyel pnömoni	İnfeksiyon etkenleri içinde %60
➢ *Streptococcus pneumoniae*	Bakteriyel pnömonilerin %70'i
➢ *Haemophilus influenzae*	Bakteriyel pnömonilerin %10'u
➢ *Staphylococcus aureus*	Bakteriyel pnömonilerin %9'u
PCP	İnfeksiyon etkenleri içinde %20
Mikobakteriler	İnfeksiyon etkenleri içinde %18
➢ *Mycobacterium tuberculosis*	Mikobakterilerin %80'i
➢ *Mycobacterium kansasii*, MAC	Mikobakterilerin %20'si
Virüsler (CMV, İnfluenza, Parainfluenza, RSV)	İnfeksiyon etkenleri içinde %5
Mantarlar (*Cryptococcus*, *Aspergillus fumigatus*)	İnfeksiyon etkenleri içinde %2
Parazitler (*Toxoplasma gondii*)	İnfeksiyon etkenleri içinde %0.5

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PAakciğer grafisi yada CT anarmallikleri	Akut veya subakut başlangıç	Kronik başlangıç
Fokal konsolidasyon	Herhangi bir mo, özellikle piyogenik bakteri Legionella infeksiyonu	Mikobakteri infeksiyonları Nokardiyoz Fungal infeksiyonlar
Diffüz interstisyel infiltrasyon	PCP Bakteriyel infeksiyonlar İnfluenz a CMV	Mikobakteri infeksiyonları Kriptokok infeksiyonlar Toksoplazmozis CMV
Nodul	Tüberküloz Kriptokok infeksiyonları	Nokardiyoz Fungal infeksiyonlar
Adenopati	Tüberküloz	Mikobakteri infeksiyonları Endemik fungal infeksiyonlar

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PAakciğer grafisi yada CT anarmallikleri	Akut veya subakut başlangıç	Kronik başlangıç
Kaviter infiltrasyon	Tüberküloz Fungal infeksiyonlar Anaerob infeksiyonlar *Pseudomonas aeruginosa* Legionella infeksiyonu	Mikobakteri infeksiyonları Nokardiyoz Fungal infeksiyonlar *Rhodococcus equi*
Plevral effüzyon	Piyojenik bakteri infeksiyonu Fungal infeksiyonlar Tüberküloz	Fungal infeksiyonlar Nokardiyoz
Pnömotoraks	PCP	

Part IV Clinical Management and Treatment of HBV and HCV Co-infection in HIV-positive Persons

Screening

1. All HIV-positive persons should be screened for HCV at time of HIV diagnosis and annually thereafter. Screening should use an anti-HCV antibody test. A positive result should be followed by HCV-RNA and genotype determination. Alternatively, HCV core-antigen testing can be performed to establish chronic HCV infection. Persons with risk factors like ongoing IDU, "chem sex" (sex under the influence of recreational drugs taken predominantly intravenously immediately before and/or during sexual contacts), mucosal traumatic sex, ongoing unprotected anal intercourse, recent sexually transmitted infection) with unexplained increase in hepatic transaminases and a negative anti-HCV antibody test should be tested for HCV-RNA for early detection of a recent infection. HCV-RNA testing is also recommended in persons with high risk factors for HCV re-infection after successful treatment or spontaneous clearance.
2. HIV-positive persons should be screened for HAV and HBV. Persons who are anti-HBc positive and HBsAg negative, in particular those with elevated liver transaminases, should be screened for HBV-DNA in addition to HBsAg to rule out occult HBV infection.
3. Hepatitis Delta antibodies should be screened for in all HBsAg positive persons.
4. HCC screening is indicated in all cirrhotic HBV or HCV co-infected persons. In HBV-infected non-cirrhotics, HCC screening should be performed in those who ever had chronic hepatitis (elevated transaminases) or with risk factors for HCC (including family history of HCC, Asians, Africans, see http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/management-of-hepatocellular-carcinoma-easl-eorto-clinical-practice-guidelines. On a case-by-case basis, omitting HCC screening can be discussed in those without risk factors and normal transaminases before starting HBV-active treatment, see page 38 and 56. Routine screening is also advised for oesophageal varices in co-infected persons with liver cirrhosis, see page 55.

Vaccination, see page 64

5. Persons lacking anti-HAV IgG antibodies or anti-HBs antibodies should be offered vaccination for the respective virus to prevent infection regardless of their CD4 count. The response to the HBV vaccine is influenced by the CD4 count and level of HIV-VL. In persons with low CD4 count (< 200 cells/µL) and ongoing HIV replication, ART should be initiated first, prior to respective vaccination. Because of the lack of data on the impact of immunisation in isolated anti-HBc IgG positive persons (HBsAg negative, anti-HBc positive and anti-HBs negative profile), vaccination is not presently recommended in this population. Additional data awaited.
6. In HIV-positive persons vaccinated for HBV with insufficient response (anti-HBs < 10 IU/L), re-vaccination should be considered. Double-dose (40 µg) at 3-4 time points (months 0, 1, 6 and 12) may help to improve response rates to the HBV vaccine. Persons who fail to seroconvert after HBV vaccination and remain at risk for HBV should have annual serological tests for evidence of HBV infection. TDF based cART has been associated with prevention of HBV infection in these persons and ART including TDF or TAF is recommended.

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Diagnostic Procedures for HCV in Persons with HCV/HIV Co-infection

Diagnosis of HCV
HCV-Ab (turn positive 1-6 months after infection as late seroconversions have been described, may rarely be lost due to immunosuppression)
HCV-RNA levels[i]
Evaluation of concurrent causes of liver disease and/or extra-hepatic HCV disease
Alcohol consumption, cardiac disease, renal impairment, autoimmunity, genetic or metabolic liver diseases (e.g. genetic haemochromatosis, diabetes mellitus or obesity) and drug-induced hepatotoxicity
Status of liver damage
Staging of fibrosis (e.g. FibroScan, liver biopsy, serum fibrosis markers[ii])
Complete blood count, ALT, AST, GGT, ALP, hepatic synthetic function (e.g. coagulation, albumin, cholinesterase)
Ultrasound every 6 months if cirrhosis (gastroscopy upon diagnosis of cirrhosis and every 3-4 years thereafter according to presence of ongoing liver disease if negative for oesophageal varices), see page 55
Before IFN-free HCV treatment
HCV genotype (GT)[iii], HCV-RNA, renal and liver function tests
Monitoring of IFN-free HCV treatment
Differential blood count, creatinine, liver enzymes at week 2. In persons with significant fibrosis (≥ F2) differential blood count, creatinine, liver enzymes, bilirubin, albumin and INR every 2-4 weeks.
HCV-RNA at 2-4 weeks and whenever needed in order to assess compliance and/or breakthrough in persons experienced to oral DAAs at end-of-treatment and at week 12 after treatment cessation (to assess SVR). In persons receiving all oral DAA therapy no association between viral load at any given time-point during therapy and SVR has yet been found.
CD4 count and HIV-VL every 12 weeks

i There is no standard conversion formula for converting the amount of HCV-RNA reported in copies/mL to the amount reported in IU/mL. The conversion factor ranges from about one to five HCV-RNA copies per IU/mL.

ii Serum fibrosis markers include APRI, FIB-4, Hyaluronic acid, Fibrometer, Fibrotest, Forns, Hepascore and other indices; recently more complex tests such as Fibrometer, Fibrotest and Hepascore have shown to more accurately predict liver fibrosis than simple biochemical tests such as APRI, FIB-4 or Forns.

iii Re-test for GT and sub-type should be performed in persons with tests carried out before second-generation tests were available (second-generation line-probe assay or real-time PCR assay) or in persons at risk of 'super-infection' for whom the GT/sub-type should be performed on most recent available specimen.

See online video lectures HCV/HIV Co-infection-Part 1, HCV/HIV Co-infection-Part 2 and HCV/HIV Co-infection-Part 3 from the EACS online course Clinical Management of HIV.

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Treatment of HCV in Persons with HCV/HIV Co-infection

Treatment indication

1. Every person with HCV/HIV co-infection should be considered for IFN-free anti-HCV treatment regardless of liver fibrosis stage.
2. Due to similar HCV cure rates and tolerability in HCV/HIV co-infected persons as in HCV mono-infected persons under DAA therapy, treatment indication and regimens are to be the same as in HCV mono-infection.
3. Re-test for GT and sub-type should be performed in persons with tests carried out before second-generation tests were available (second-generation line-probe assay or real-time PCR assay) or in persons at risk of 'super-infection' for whom the GT/sub-type should be performed on the most recent available specimen.

Treatment selection

4. IFN-free DAA combinations are now standard of care for chronic HCV see HCV Treatment Options in HCV/HIV Co-infected Persons. IFN-containing HCV regimens are no longer recommended. For diagnostics and management of IFN-containing HCV regimens please refer to previous versions of these Guidelines, available online at http://www.eacsociety.org/files/guidelines_8.2-english.pdf.
5. Selection of DAA combinations is based upon HCV GT, stage of liver fibrosis, pre-treatment history and resistance-associated substitutions (RAS) if tested.
6. Use of older, first generation HCV PIs (boceprevir and telaprevir; only indicated in GT1) are no longer recommended because of increased toxicities. The second generation PI simeprevir can cause hyperbilirubinaemia and skin reactions/photosensibility.
7. Due to drug-drug interactions in particular HIV and HCV PIs careful checking for interactions is urgently recommended prior to starting HCV therapy, see Drug-drug Interactions between DAAs and ARVs or http://www.hep-druginteractions.org.
8. In persons failing a first course with DAAs, current re-treatment strategies should include at least 2 active drug classes according to resistance testing results with a preferential use of one drug with high genetic barrier to resistance and with extended treatment durations and addition of RBV. Otherwise, new treatment options should be awaited if deferred treatment can be justified and in presence of relevant RASs at failure. In persons with decompensated cirrhosis, usage of SOF/VEL without protease inhibitors in combination with RBV for 24 weeks could be considered. In order to facilitate the best choice of HCV therapy before starting re-treatment, HCV resistance testing should be repeated (only in the gene with previous RASs) and should be based on population sequencing with a 15% detection cut-off. Shorter treatment duration (8 weeks in non-cirrhotics and 12 weeks in compensated cirrhotics) without RBV can be used in persons never treated with NS5A inhibitors and not infected with HCV GT 3; all other persons should be treated for at least 16 weeks; addition of SOF to GLE/PIB could be considered in those already treated with NS3 and NS5A inhibitors according to resistance testing. If available, SOF/VEL/VOX should be used for 12 weeks without RBV in all persons without decompensated cirrhosis.

HCV Treatment Options in HCV/HIV Co-infected Persons

IFN-free HCV Treatment Options

HCV GT	Treatment regimen	Treatment duration & RBV usage		
		Non-cirrhotic	Compensated cirrhotic	Decompensated cirrhotics CTP class B/C
1 & 4	SOF + SMP +/- RBV	GT 4 only: 12 weeks with RBV or 24 weeks without RBV[i]		Not recommended
	SOF/LDV +/- RBV	8 weeks without RBV[ix] or 12 weeks +/- RBV[xi]	12 weeks with RBV[xii]	
	SOF + DCV +/- RBV	12 weeks +/- RBV[iii]	12 weeks with RBV[xii]	
	SOF/VEL	12 weeks		12 weeks with RBV
	SOF/VEL/VOX	8 weeks[viii]	12 weeks	Not recommended
	OBV/PTV/r + DSV	8[x]-12 weeks in GT 1b	12 weeks in GT 1b	Not recommended
	OBV/PTV/r + DSV + RBV	12 weeks in GT 1a	24 weeks in GT 1a	Not recommended
	OBV/PTV/r + RBV	12 weeks in GT 4		Not recommended
	EBR/GZR	12 weeks[vi]		Not recommended
	GLE/PIB	8 weeks	12 weeks	Not recommended
2	SOF + DCV	12 weeks		12 weeks with RBV
	SOF/VEL	12 weeks		12 weeks with RBV
	SOF/VEL/VOX	8 weeks[viii]	12 weeks	Not recommended
	GLE/PIB	8 weeks	12 weeks	Not recommended
3	SOF + DCV +/- RBV	12 weeks +/- RBV[xiii] or 24 weeks without RBV	24 weeks with RBV	
	SOF/VEL +/- RBV	12 weeks +/- RBV[xiii] or 24 weeks without RBV		24 weeks with RBV
	SOF/VEL/VOX	8 weeks[xiii]		Not recommended
	GLE/PIB	8 weeks[ix]	12 weeks[ix]	Not recommended
5 & 6	SOF/LDV +/- RBV	12 weeks +/- RBV or 24 weeks without RBV[i]	12 weeks with RBV[xii]	
	SOF + DCV +/- RBV	12 weeks +/- RBV or 24 weeks without RBV[i]	12 weeks with RBV[xii]	
	SOF/VEL	12 weeks		12 weeks with RBV
	SOF/VEL/VOX	8 weeks[viii]	12 weeks	Not recommended
	GLE/PIB	8 weeks	12 weeks	Not recommended

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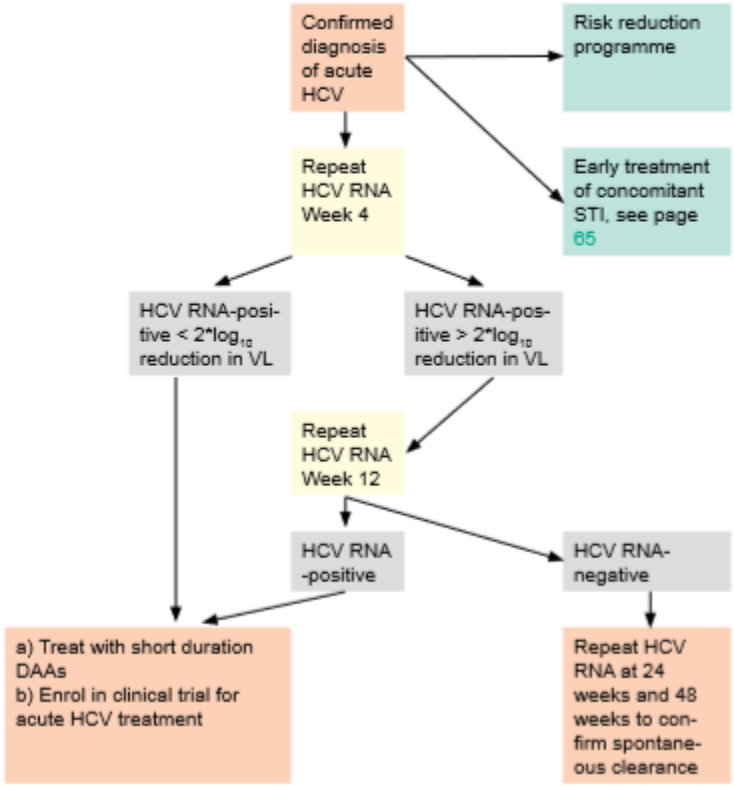
DCV = daclatasvir
DSV = dasabuvir
EBR = elbasvir
GLE = glecaprevir
GZR = grazoprevir
LDV = ledipasvir
OBV = ombitasvir
PIB = pibrentasvir
PTV/r = paritaprevir/RTV
RBV = ribavirin
SMP = simeprevir
SOF = sofosbuvir
VEL = velpatasvir
VOX = voxilaprevir
RAS = resistance associated substitutions

Algorithm for Management of Acute HCV in Persons with HCV/HIV Co-infection



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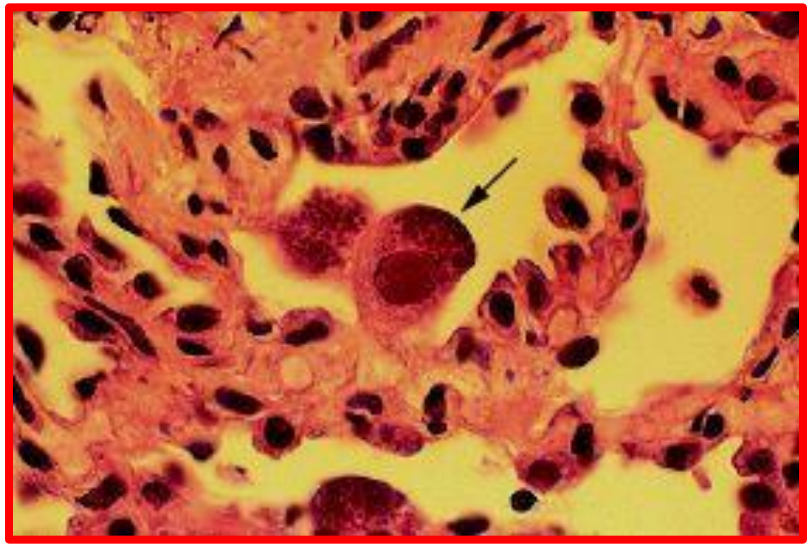
CMV TANISAL YAKLAŞIM

- CMV pnömonisi nadir
- Tanısı zor
- Klinik bulgular
  - Ateş
  - Öksürük
  - Dispne
- Radyolojik bulgular
  - Diffüz interstisyal infiltrasyon
- Diğer patojenlerin saptanmaması

CMV-TANISAL YAKLAŞIM

- **CMV PCRpozitifliği veya BAL'dan kültür**
- **CMV antijenemi testi pozitifliği**
  - **Duyarlılığı %50-61**
- **Akciğer biyopsisinde pnömonitis ve sitopatik etkinin gösterilmesi**
  - **BALkültürü ve CMV PCR'den daha spesifik**



Salomon N. AIDS. 1997
Wallace JM, Chest. 1987
Uberti-Foppa C.Chest. 1998
Hayner CE, Chest. 1995

CMV

CMV için risk faktörleri

- CD4 sayısı <50 hücre/mm^3 olması
- Hastanın ART almaması veya ART'ye cevabın iyi olmaması
- PCR ile yüksek CMV viremisi saptanması
- HIV-RNA >100000 IU/ml olması

Jabs DA. Am J Opthalmol 2002;133:48-61

- CMV IgG pozitifliği: Risk faktörü
- Latent infeksiyonun reaktivasyonu

CMV

- HIV infekte hastalarda CMV'nin sinir sistemi tutulumuna bağlı
  - Ventriküloensefalit (konfüzyon, fokal nörolojik defisit, kraniyal sinir tutulumu, nistagmus, ataksivb)
  - Poliradikülomyelopati
  - Demans

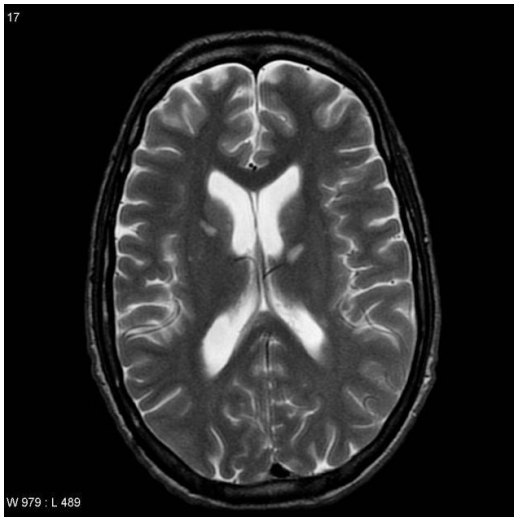
CMV

- CMV nörolojik hastalığı tanısı
  - Klinik bulgular
  - Görüntüleme
  - PCR ile BOS'ta ve beyin dokusunda CMV'nin gösterilmesi (%80), sensitivite ve spesifite yüksek
  - BOS'ta lenfositik pleositoz, protein normal veya yüksek

MR

- Periventriküler kontrast tutulumu
- Ventrikülit, menenjit, enfarkt,
- Hidrosefali, serebral atrofi

Cinque P. J Neurovirol 1998;4:120-32



CMV tedavi

- Gansiklovir (5 mg/kg iv) 2x1
- Foskarnet (90 mg/gün iv) 2x1
- Optimal tedavi süresi net değil

Cytomegalovirus (CMV) infections

Treatment			
Diagnosis of retinitis: clinical appearance of typical retinal lesions AND response to therapy. PCR of aqueous and vitreous humor optional **Diagnosis of esophagitis / colitis:** endoscopic presence of ulcerations AND typical histopathological picture (cellular / nuclear inclusion bodies) **Diagnosis of encephalitis / myelitis:** clinical appearance AND positive PCR in CSF Antibody testing and PCR in blood not useful for diagnosis of end-organ disease			
	Drug	**Dose**	**Comments**
Retinitis, immediate sight-threatening lesions	**ganciclovir**	2 x 5 mg/kg/day iv	21 days, then secondary prophylaxis
	or **foscarnet**	2 x 90 mg/kg/day iv	
Retinitis, small peripheral retinal lesions	**valganciclovir**	2 x 900 mg/day po (with food)	14-21 days, then secondary prophylaxis
	or **foscarnet**	2 x 90 mg/kg/day iv	
	or **cidofovir** **+ probenecid** **+ NaCl 0.9% hydration**	1 x 5 mg/kg/week iv	2 weeks then every 2 weeks. Cidofovir may not be available in all European countries
Oesophagitis/Colitis	**ganciclovir**	2 x 5 mg/kg/day iv	Treat 3-6 weeks, respectively until symptoms resolved
	or **foscarnet**	2 x 90 mg/kg/day iv	
	or **valganciclovir**	2 x 900 mg/day po (with food)	In milder disease if oral treatment tolerated
Encephalitis/Myelitis	**ganciclovir and / or** **foscarnet**	2 x 5 mg/kg/day iv 2 x 90 mg/kg/day iv	Treat until symptoms resolved and CMV replication in CSF has cleared (negative PCR in CSF) Treatment is individualised according to clinical symptoms and response to treatment

Spectral domain optical coherence tomography and fundus autofluorescence findings in cytomegalovirus retinitis in HIV-infected patients

Shigeko Yashiro[1] · Takeshi Nishijima[2] · Yuuka Yamamoto[1] · Yumi Sekine[1] · Natsuyo Yoshida-Hata[1] · Tomohiro Iida[3] · Shinichi Oka[2]

Received: 28 June 2017 / Accepted: 21 January 2018

Abstract

Purpose To
(FAF) findin
Study design
Methods Th
ophthalmolo
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Results In th
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and highly c
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epithelium. I
Conclusion Although the number of examined eyes was limited, SD-OCT and FAF provide new information in various stages of CMV retinitis in patients with HIV infection that is not obtainable by conventional examination and which may be of great benefit when screening for the initial stage of CMV retinitis.

CMV Retiniti, göz ardı edilmemesi gereken bir hastalıktır.

HIV hastalarına tanı konulduğu dönemde mutlaka retinal tarama yapılması gerektiğini unutmamak gerek.

The Effect of Human Immunodeficiency Virus and Cytomegalovirus Infection on Infant R

Marz 2018

HIV ile enfekte anneden doğmuş bebeklerde gelişen CMV enfeksiyonu infant aşılamanın etkinliğini değiştirir mi?

HIV ile enfekte olan bebeklerde bu farkın klinik önemi bilinmemekle birlikte tetanos, difteri, boğmaca, hepatit B ve pnömokokkal aşılamadan sonra aşı ile indüklenen antikor konsantrasyonları daha düşük olduğu saptandı.

leads to an increase in activation and differentiation of the whole T-cell population, but there is limited data on the effects of CMV infection on infant vaccine responses. In light of growing evidence of poor clinical outcomes associated with CMV infection in HIV-exposed, uninfected infants, further studies are particularly important in this group. A clearer understanding of the mechanisms by which maternal viral infections influence the developing infant immune system is critical to the success of maternal and infant vaccination strategies.

HSV ENFEKSİYONU

Herpes simplex virus (HSV) infections

Treatment			
Diagnosis: antigen testing / PCR / culture of swab / CSF / biopsy. Clinical appearance of skin lesions not reliable			
	Drug	**Dose**	**Comments**
Initial genital / mucocutaneous HSV	**valaciclovir**	2 x 1000 mg/day po	7-10 days or until lesions healed
	or **famciclovir**	2 x 500 mg/day po	7-10 days or until lesions healed
	or **aciclovir**	3 x 400-800 mg/day po	7-10 days or until lesions healed
Recurrent genital / mucocutaneous HSV (> 6 episodes/year)	**valaciclovir**	2 x 500 mg/day po	Chronic suppressive therapy. Alternatively start early treatment as above if recurrences occur
Severe mucocutaneous lesions	**aciclovir**	3 x 5 mg/kg/day iv	After lesions begin to regress, switch to oral treatment until lesions have healed
Encephalitis	**aciclovir**	3 x 10 mg/kg/day iv	14-21 days
Aciclovir resistant mucocutaneous HSV infection	**foscarnet**	2-3 x 80-120 mg/kg/day iv	Until clinical response

Varicella zoster virus (VZV) infections

Treatment			
Diagnosis: typical clinical appearance with/without antibody testing, OR antigen testing / PCR / culture of swab / CSF / biopsy			
	Drug	**Dose**	**Comments**
Primary Varicella infection (Chickenpox)	**valaciclovir**	3 x 1000 mg/day po	5-7 days
Herpes Zoster (Shingles): Not disseminated	**valaciclovir**	3 x 1000 mg/day po	7-10 days
	or **famciclovir**	3 x 500 mg/day po	7-10 days
Herpes Zoster: Disseminated	**aciclovir**	3 x 10 mg/kg/day iv	10-14 days
Encephalitis (including vasculitis)	**aciclovir**	3 x 10-15mg/kg/day	14-21 days

Teşekkür Ederim

HIV/AIDS KAMPI

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OLGULAR ESLIGINDE ZOR VAKALARIN YONETIMI