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Chapter 9

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 9

Infectious diseases

Complications • pneumonia, seizures, and encephalopathy • A rare complication is a hemiseizure-hemiplegia syndrome, which is thought to be related to post-immunisation hyperthermia rather than direct neurological toxicity. Treatment • Treatment is largely supportive, but antibiotics can reduce the duration of symptoms. • Erythromycin, clarithromycin and azithromycin are first choice Prevention • The pertussis vaccine is estimated to be 63% to 94% effective in the diphtheria-pertussistetanus (DPT) shot

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Acute epiglottitis Overview • Acute epiglottitis is rare but serious infection caused by Haemophilus influenzae type B. • Prompt recognition and treatment is essential as airway obstruction may develop. • Epiglottitis was generally considered a disease of childhood but in the UK it is now more common in adults due to the immunisation programme. • The incidence of epiglottitis has decreased since the introduction of the Hib vaccine Features • Rapid onset • High temperature, generally unwell • Stridor • Drooling of saliva (the most specific sign) Diagnosis • the preferred method of diagnosis →direct visualization of the epiglottis using nasopharyngoscopy/laryngoscopy →cherry-red epiglottis No attempt should be made to visualise the epiglottis until an anaesthetist is present as there is a high risk of causing acute airway obstruction by touching the inflamed tissue. • Lateral neck soft-tissue radiography useful screening tool in suspected stable patient. Only 79% of epiglottis cases are diagnosed by neck soft-tissue radiographs The classic findings are: swollen epiglottis (ie, a thumb sign), thickened aryepiglottic folds, and obliteration of the vallecula (pre-epiglottic space). (vallecula sign). The vallecula is the air pocket found at the level of the hyoid bone just anterior to the epiglottis. • blood culture Differential • cough is specific for croup • drooling is specific for epiglottitis • laryngomalacia improves in the prone position Treatment • Unstable patients →immediate airway management. Early intubation is essential, especially in cases where there is respiratory distress. • Third generation cephalosporin is the treatment of choice. • Close contacts of patients in whom Haemophilus influenzae type b is isolated should receive rifampin prophylaxis (20 mg/kg; not to exceed 600 mg/d for 4 d).

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• Recurrent episodes of acute epiglottitis in adults is unusual and, when present, warrants immune system investigation. Haemophilus influenzae requires hemin (factor X) and NAD+ (factor V) for growth. Other Haemophilus species require only NAD+ and therefore grow on blood agar. Haemophilus influenzae: culture requirements: Read Hemophilus as "HemoFive": · Needs Heme with Factors Five and Ten.

Cellulitis Cellulitis • Staphylococcus aureus and Streptococci are the commonest causative organisms. • Group B Streptococcus has a predilection for diabetic patients Definition • inflammation of the skin and subcutaneous tissues, Causes • Staphylococcus aureus and Streptococci are the commonest causative organisms. • Group B Streptococcus has a predilection for diabetic patients and is the likeliest causative organism in diabetics Features • commonly occurs on the shins • erythema, pain, swelling • systemic upset such as fever • Cellulitis does not have sharp, well-defined borders, unlike an erysipelas infection. Eron classification NICE Clinical Knowledge Summaries recommend we use the Eron classification to guide how we manage patients with cellulitis: Class Features I There are no signs of systemic toxicity and the person has no uncontrolled co-morbidities II The person is either systemically unwell or systemically well but with a co-morbidity (for example peripheral arterial disease, chronic venous insufficiency, or morbid obesity) which may complicate or delay resolution of infection III The person has significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension, or unstable co-morbidities that may interfere with a response to treatment, or a limb-threatening infection due to vascular compromise IV The person has sepsis syndrome or a severe life-threatening infection such as necrotizing fasciitis Management • Criteria for admission for intravenous antibiotics Eron Class III or Class IV cellulitis. severe or rapidly deteriorating cellulitis (for example extensive areas of skin). very young (under 1 year of age) or frail. immunocompromised. significant lymphoedema.

 facial cellulitis (unless very mild) or periorbital cellulitis. • Management Eron Class II cellulitis: • Admission may not be necessary if the facilities and expertise are available in the community to give intravenous antibiotics and monitor the person. • Other patients can be treated with oral antibiotics. • Antibiotics mild/moderate cellulitis First line flucloxacillin (BNF recommendation) first choice to treat sensitive staphylococcal infections MRSA is resistant to flucloxacillin in patients allergic to penicillin Clarithromycin or clindamycin. in patients who have failed to respond to flucloxacillin oral clindamycin The most appropriate treatment is clindamycin and flucloxacillin, which covers the majority of organisms responsible for cellulitis. Flucloxacillin is bactericidal for both Staphylococcus and Streptococcus, whereas clindamycin has an anti-toxin effect for both these groups of organisms (in addition to Clostridium perfringen). Their effect is therefore synergistic, and they should be used together where rapid control is required (e.g. in finger cellulitis) or in severe cases Although clindamycin is a bacteriostatic antibiotic, it acts by switching off protein synthesis within bacteria; this in turn will lead to decreased exotoxin expression, thereby removing the mediators of toxic shock syndrome (TSS). If no significant

improvement within 48 hours, the patient should be readmitted for intravenous antibiotics. Severe cellulitis should be treated with intravenous benzylpenicillin + flucloxacillin. If there is any suspicion of tendon involvement (Intact joint movements make this less likely) the plastics or orthopaedics team should be asked to review and intravenous antibiotics initiated.

Methicillin-resistant Staphylococcus aureus (MRSA) Epidemiology • In many hospitals, 40%-50% of the S. aureus isolates are resistant to methicillin Mechanism of resistance • Penicillin binding proteins are the characteristic mutated proteins in methicillinresistant Staphylococcus aureus. • The resistant organisms produce penicillin-binding proteins (PBPs) that have a low affinity for binding beta-lactamase antibiotics (Modification of target penicillin-binding proteins). Other organisms which do the same are Pneumococci and Enterococci. Who should be screened for MRSA? • all patients awaiting elective admissions exceptions include: terminations of pregnancy ophthalmic surgery Patients admitted to mental health trusts. • all emergency admissions. Where is the site of most concern for staff carriage of MRSA?

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• The nose is the area of carriage for MRSA which gives most area for concern with respect to carriage by staff. How should a patient be screened for MRSA? • nasal swab and skin lesions or wounds the swab should be wiped around the inside rim of a patient's nose for 5 seconds the microbiology form must be labelled 'MRSA screen' Suppression of MRSA from a carrier once identified • nose: mupirocin 2% in white soft paraffin, TDS for 5 days • skin: chlorhexidine gluconate, OD for 5 days. Apply all over but particularly to the axilla, groin and perineum Treatment of MRSA infections • Vancomycin → the first line • Teicoplanin • Linezolid Linezolid is the only oral medication available against MRSA. • Ceftaroline fifth generation cephalosporin Ceftaroline is the only cephalosporin to cover MRSA. • Some strains may be sensitive to the antibiotics listed below but they should not generally be used alone because resistance may develop: rifampicin macrolides tetracyclines aminoglycosides clindamycin • Relatively new antibiotics such as linezolid, quinupristin /dalfopristin combinations and tigecycline have activity against MRSA but should be reserved for resistant cases MRCPUK-part-1-January-2009: What is the most effective single step to reduce the incidence of MRSA? Hand hygiene MRCPI-part-1-jan-2017: What is the most appropriate antibiotic regimen for possible line sepsis from an indwelling permacath? Vancomycin + Gentamicin The antibiotic chosen should have both gram-positive and gram-negative cover, including MRSA. vancomycin and doxycycline are able to treat MRSA, but doxycycline has limited gram-negative cover, unlike gentamicin.

Necrotising fasciitis Overview • Necrotising fasciitis is a medical emergency that is difficult to recognise in the early stages. Classification (according to the causative organism): • Type 1 is caused by mixed anaerobes and aerobes (often occurs post-surgery in diabetics) • Type 2 is caused by Streptococcus pyogenes commonly caused by group A Streptococci

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Infectious diseases Features • acute onset • painful, erythematous lesions • extremely tender over infected tissue Management • urgent surgical referral debridement • intravenous antibiotics Clindamycin and Tazocin Clindamycin bacteriostatic inhibits formation of peptides bonds at 50S ribosomal subunit It is also a potent suppressor of bacterial toxin synthesis. Group A Streptocooci are usually very sensitive to benzylpenicillin so this is frequently added though this does not neutralises the toxin.

Toxic shock syndrome (TSS) Causes • Staphylococcus aureus, which releases enterotoxin type B (i.e. toxic shock syndrome toxin1), • Streptococcus pyogenes, which releases pyogenic exotoxins. Risk factors • Recent menstruation Although the earliest described cases involved mostly menstruating women using highly absorbent tampons, only 55% of current cases are associated with menstruation. • Recent use of barrier contraceptives such as diaphragms and vaginal sponges • Vaginal tampon use (especially prolonged) • Recent childbirth • Recent surgery, • Current S. aureus infection. Features • non-specific (e.g., fever, chills, myalgias, headache), • toxicity occurs early, resulting in serious life-threatening disease • Staphylococcal scalded skin syndrome Diffuse erythema that desquamates as the patient recovers Occur 10% of patients Exotoxin A is the causative toxin in staphylococcus scalded skin syndrome. most common in children but can be seen in immunocompromised adults. destroys keratinocyte attachments in the stratum granulosum, leading to a very superficial sloughing of the epidermis that heals completely. It is also known as Pemphigus neonatorum or Ritter disease. • multi-organ system failure. Staphylococcus aureus Toxic shock syndrome toxin binds to major histocompatibility complex II and T cell receptor overwhelming release of cytokines shock.

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Types • Streptococcal toxic shock syndrome (TSS) can occur with infection at any site but is more commonly associated with an infected cutaneous site. • Staphylococcal TSS (menstrual or non-menstrual) severe systemic reaction to staphylococcal exotoxins. associated with extended tampon use, postpartum infections, and other sites of infection with the organism. Diagnosis • Centers for Disease Control and Prevention diagnostic criteria fever: temperature > 38.9 C hypotension: systolic blood pressure < 90 mmHg diffuse erythematous rash desquamation of rash, especially of the palms and soles involvement of three or more organ systems: e.g. gastrointestinal (diarrhoea and vomiting), mucous membrane erythema, renal failure, hepatitis, thrombocytopenia, CNS involvement (e.g. confusion) Treatment • supportive care in an ICU, • early empirical antibiotic treatment, and further culture-sensitive antibiotic treatment. Although clindamycin is a bacteriostatic antibiotic, it acts by switching off protein synthesis within bacteria; this in turn will lead to decreased exotoxin expression, thereby removing the mediators of TSS. • Surgical debridement may be needed for deep-seated streptococcal infections.

Cholera electron microscope image of Vibrio cholerae bacteria Overview • caused by Vibro cholerae - Gram negative bacteria • Because the organism is not acid-resistant, it depends on its large inoculum size (infectious dose) to withstand gastric acidity. If ingested with water, a higher infectious dose is needed. When ingested with food, fewer organisms are required to produce disease. ↓ gastric acidity (anti-acid drugs, gastrectomy) ↑risk of cholera infection and

severity Mechanism by which cholera leads to fluid loss: • Cholera toxin has two parts, A and B.

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 B subunits are responsible for binding to a ganglioside (monosialosyl ganglioside, GM1 receptor) located on the surface of the cells that line the intestinal mucosa. B binds while A activates G protein activates adenylate cyclase ↑(cAMP) unrestricted chloride secretion from villous crypts. cholera toxin stimulates the generation of cyclic AMP as the second messenger Features • profuse 'rice water' diarrhoea • dehydration • hypoglycaemia After dehydration, hypoglycemia is the most common lethal complication of cholera in children. Management • oral rehydration therapy • antibiotics: doxycycline, ciprofloxacin

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Congenital infections The major congenital infections encountered in examinations are rubella, toxoplasmosis and cytomegalovirus Cytomegalovirus is the most common congenital infection in the UK. Maternal infection is usually asymptomatic Rubella Toxoplasmosis Cytomegalovirus Characteristic features Sensorineural deafness Congenital cataracts Congenital heart disease (e.g. patent ductus arteriosus) Glaucoma Other features Growth retardation Hepatosplenomegaly Purpuric skin lesions 'Salt and pepper' chorioretinitis Microphthalmia Cerebral palsy Notes & Notes for MRCP
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 Cerebral calcification Chorioretinitis Hydrocephalus Growth retardation Purpuric skin lesions Anaemia Hepatosplenomegaly Cerebral palsy Sensorineural deafness Encephalitis/seizures Pneumonitis Hepatosplenomegaly Anaemia Jaundice Cerebral palsy

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Chickenpox (Varicella-zoster virus) Overview • Chickenpox is caused by primary infection with varicella zoster virus. • Shingles is reactivation of dormant virus in dorsal root ganglion • Chickenpox is highly infectious (infection rate in household contacts of 90%). • spread via the respiratory route • can be caught from someone with shingles • infectivity = 4 days before rash, until 5 days after the rash first appeared* • incubation period = 10-21 days • It is commonest in spring time • Causes congenital limb deformity • HIV HIV-positive patients are more prone to herpes zoster regardless of their CD4 count. In addition to the typical dermatomal distribution of the vesicular rash, HIV patients occasionally have vesicles scattered in adjacent dermatomes. In advanced HIV disease VZV can manifest as severe disseminated disease. Clinical features (tend to be more severe in older children/adults) • fever initially • itchy, rash starting on head/trunk before spreading. Initially macular then papular then vesicular • systemic upset is usually mild Management is supportive • keep cool, trim nails • calamine lotion • school exclusion: current HPA advice is 5 days from start of skin eruption. They also state 'Traditionally children have been excluded until all lesions are crusted. However, transmission has never been reported beyond the fifth day of the rash.' • immunocompromised patients and newborns with peripartum exposure

should receive varicella zoster immunoglobulin (VZIG). If chickenpox develops then IV aciclovir should be considered Aciclovir (also famciclovir, and ganciclovir) acts through inhibition of viral (DNA) polymerase but it is a pro-drug and first requires phosphorylation by thymidine kinase. Resistance arises when the virus lacks thymidine kinase For thymidine kinase-deficient varicella-zoster virus strain: Cidofovir does not require activation by viral thymidine kinase; therefore, it would be best suited to treat the thymidine kinase-deficient varicella-zoster virus. • adults chicken pox should be treated with acyclovir within 24 hours of the appearance of rash because it can lessen the occurrence of post herpetic neuralgia. Complications • Common complication is secondary bacterial infection of the lesions. • Chicken pox in the first and second trimester can produce a syndrome of skin scarring, hypoplastic limbs, eye and central nervous system impairments. • Rare complications include Varicella pneumonia Varicella pneumonia occurs in up to 20% of adults with chickenpox, uncommon in children

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 The risk is higher in smokers and pregnancy. Features appearing three to five days into the course of the illness. Symptoms include tachypnoea, cough, dyspnoea, and fever. Cyanosis, pleuritic chest pain and haemoptysis are common. Treatment → Aciclovir Encephalitis (cerebellar involvement may be seen) Disseminated haemorrhagic chickenpox Arthritis, nephritis and pancreatitis may very rarely be seen mechanism of acyclovir resistance reduced production of viral thymidine kinase Chest x-ray showing miliary opacities secondary to healed varicella pneumonia. Multiple tiny calcific miliary opacities noted throughout both lungs. These are of uniform size and dense suggesting calcification. There is no focal lung parenchymal mass or cavitating lesion seen.The appearances are characteristic for healed varicella pneumonia. *it was traditionally taught that patients were infective until all lesions had scabbed over Chickenpox exposure in pregnancy Chickenpox exposure in pregnancy - first step is to check antibodies • In pregnancy there is a risk to both the mother and also the fetus, a syndrome now termed fetal varicella syndrome Risks to the fetus and neonate relate to the time of infection: • Less than 20 weeks pregnancy:

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 congenital varicella (limb hypoplasia, microcephaly, cataracts, growth retardation, skin scarring). High mortality. The incidence of congenital varicella syndrome is about 2% in mothers who develop primary chickenpox in the first half of the pregnancy. • Second to third trimester: herpes zoster in an otherwise healthy infant. • Minus seven days to plus seven days after delivery: severe and even fatal disease (30% mortality). Risks to the mother • 5 times greater risk of pneumonitis Fetal varicella syndrome (FVS) • risk of FVS following maternal varicella exposure is around 1% if occurs before 20 weeks gestation • studies have shown a very small number of cases occurring between 20-28 weeks gestation and none following 28 weeks • features of FVS include skin scarring, eye defects (microphthalmia), limb hypoplasia, microcephaly and learning disabilities Other risks to the fetus • shingles in infancy: 1-2% risk if maternal exposure in the second or third

trimester • severe neonatal varicella: if mother develops rash between 5 days before and 2 days after birth there is a risk of neonatal varicella, which may be fatal to the newborn child in around 20% of cases Management of chickenpox exposure • if there is any doubt about the mother previously having chickenpox maternal blood should be urgently checked for varicella antibodies • if the pregnant women is not immune to varicella she should be given varicella zoster immunoglobulin (VZIG) as soon as possible. RCOG and Greenbook guidelines suggest VZIG is effective up to 10 days post exposure • consensus guidelines suggest oral aciclovir should be given if pregnant women with chickenpox present within 24 hours of onset of the rash Varicella zoster immunoglobulin (VZIG) • prepared from pooled plasma of UK blood donors with a history of recent chickenpox or herpes zoster. • Donors are screened for HIV, hepatitis B and hepatitis C. • VZIG prophylaxis is recommended for patients who fulfil all the following criteria:

1. A clinical condition that increases the risk of severe varicella, (for example, immunosuppression, neonates, pregnant women)
2. No antibodies to varicella zoster
3. Significant exposure to chickenpox or herpes. • VZIG prophylaxis is of no benefit if chickenpox has already developed. • Severe or fatal varicella can occur despite VZIG prophylaxis. Active immunisation should therefore be used for susceptible immunosuppressed patients at long term risk.

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Cytomegalovirus Overview • Cytomegalovirus (CMV, HHV-5), is one of the herpes viruses. • Herpes viridae is the family of viruses to which cytomegalovirus belongs. • Double stranded DNA virus. • Mononuclear cells are the class of leukocytes in which cytomegalovirus lies dormant. • It is thought that around 50% of people have been exposed to the CMV virus although it only usually causes disease in the immunocompromised, for example people with HIV or those on immunosuppressants following organ transplantation. Diagnosis • infected cells have a 'Owl's eye' appearance due to intranuclear inclusion bodies Patterns of disease • Congenital CMV infection features include growth retardation, pinpoint petechial 'blueberry muffin' skin lesions, microcephaly, sensorineural deafness, encephalitis (seizures) and hepatosplenomegaly • CMV mononucleosis infectious mononucleosis-like illness may develop in immunocompetent individuals • CMV retinitis common in HIV patients with a low CD4 count (< 50) presents with visual impairment e.g. 'blurred vision'. Fundoscopy shows retinal haemorrhages and necrosis, often called 'pizza' retina IV ganciclovir is the treatment of choice Valganciclovir is an oral pro-drug for ganciclovir, with similar bioavailability but without the need to deliver it IV, making it the preferred option here. The efficacy of valganciclovir is similar to ganciclovir without the need for IV administration, and this drives ganciclovir as the option where oral therapy isn’t tolerated. The toxicity profile for valganciclovir is the same as that for ganciclovir, with bone marrow suppression the main concern. Foscarnet is the drug of choice for ganciclovir-resistant cytomegalovirus retinitis. • CMV encephalopathy: seen in patients with HIV who have low CD4 counts • CMV pneumonitis • CMV colitis HIV+ bloody diarrhea+ no abdominal pain +normal stool examination Do Colonoscopy to

diagnose CMV colitis Patients with inflammatory bowel disease are at increased risk of CMV colitis particularly those on immunosuppression. COLONOSCOPY finding multiple ulcer and mucosal erosion The most appropriate investigation is Flexible sigmoidoscopy and biopsy in severe colitis endoscopy should be limited to flexible sigmoidoscopy only due to an increased risk of perforation. Biopsy shows: cytomegalic cell+ intranuclear inclusion body

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Dengue fever Definition • Dengue fever is a viral infection which can progress to viral haemorrhagic fever (also yellow fever, Lassa fever, Ebola) Pathogen • caused by Dengue virus , RNA virus of the genus Flavivirus • Transmitted by the Aedes aegyti mosquito • Incubation period 4-10 days. If symptoms appear more than 2 weeks after returning from a dengue-endemic region, it is very unlikely that dengue is the cause. Epidemiology • Distribution: tropical regions worldwide, particularly Asia (e.g., Thailand) • Most common viral disease affecting tourists in tropical regions Features • headache (often retro-orbital) • fever • myalgia (severe musculoskeletal pain is a prominent feature) hence the name breakbone fever. • pleuritic pain • facial flushing (dengue) • maculopapular rash (confluent erythematous rash over the precordium) When the patient is near recovery there may develop a maculopapular rash beginning on the trunk and spreading to the extremities and the face. • There is often adenopathy, palatal vesicles and sclera injection on the first day. • Epistaxis and scattered petechiae may be observed. Complication • a form of disseminated intravascular coagulation (DIC) known as dengue haemorrhagic fever (DHF) may develop. Around 20-30% of these patients go on to develop dengue shock syndrome (DSS) Laboratory tests • Leukopenia • Neutropenia • Thrombocytopenia • ↑ AST • Hct significantly increased or decreased in DHF (due to plasma leakage) Diagnosis • diagnosed by dengue fever serology. Treatment • symptomatic e.g. fluid resuscitation, blood transfusion etc

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Herpes simplex virus Pathogen • Herpes simplex virus is a DNA virus. • There are two strains of the herpes simplex virus (HSV) in humans:

1. HSV-1 → most commonly cause orofacial disease
2. HSV-2 → most commonly cause genital disease. • Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap • Worldwide seroprevalence is high, with antibodies detectable in over 90% of the population. Of these cases, approx. 60% are caused by HSV-1. • Incubation period →2 days to 2 weeks. Pathophysiology • Inoculation: The virus enters the body through mucosal surfaces or small dermal lesions. • Neurovirulence: The virus invades, spreads, and replicates in nerve cells. • Latency: After primary infection, the virus remains dormant in the ganglion neurons. Trigeminal ganglion: HSV-1 Sacral ganglion: HSV-2 • Reactivation: triggered by various factors (e.g., immunodeficiency,

stress, trauma) → clinical manifestations • Dissemination Infection spreads to unusual sites (e.g., lungs, gastrointestinal tract, eyes) May occur in pregnant patients or patients with severe immunodeficiency • Recurrent attacks tend to be shorter and less severe. Transmission • Only from direct contact with mucosal tissue or secretions of another infected person • Because the virus dies quickly outside of the body, it's nearly impossible to get the infection through contact with toilets, towels or other objects used by an infected person • Infection with HSV-1 usually is acquired in childhood via saliva. • HSV-2 is mostly spread through genital contact Features Herpes zoster usually has a prodrome pain before the vesicles appear. It usually follows a particular dermatome but in immune suppression the disease may affect more than one dermatome. Herpes simplex II is the wrong answer. Herpes simplex II vesicles may appear, but they never follow a particular dermatome. • Up to 80% of herpes simplex infections are asymptomatic. • Labial herpes (herpes labialis) Pathogen →Mostly HSV-1 Recurring, erythematous vesicles that turn into painful ulcerations, also known as cold sores; oral mucosa and lip borders In orofacial HSV infections, the trigeminal ganglia are most commonly involved • Herpetic gingivostomatitis Mainly in children (~1–6 years), but also immunocompromised patients

 Erythema and painful ulcerations on perioral skin and oral mucosa • Genital herpes (herpes genitalis) → painful genital ulceration Pathogen → HSV-2 Blistering and ulceration of the external genitalia or perianal region (cervix/rectum) → “punched-out” ulcer Painful lymphadenopathy in the groin area (tender inguinal lymphadenitis, usually bilateral.) In genital HSV infection, the sacral nerve root ganglia (S2-S5) are involved. • Eczema herpeticum associated with preexisting skin conditions, most often atopic dermatitis Fever, malaise, lymphadenopathy Extensive disseminated and painful eruptions on the head and upper body; erythematous skin with multiple, round, umbilicated vesicles • Herpetic whitlow Pathogen → HSV-1 in 60% of cases; HSV-2 in 40% of cases (in the adult population) Aetiology → Direct contact with infected secretions Risk factors Children (via sucking of thumb/fingers (may have a history of labial herpes) Health care workers exposed to oral secretions (e.g., dentists) Incubation period: 2–20 days Infection of the dermal and subcutaneous tissue Grouped, non-purulent vesicles on an erythematous base, may rupture or ulcerate, involved one or more fingers (especially the thumb and index fingers); mostly found on terminal phalanx. Axillary and epitrochlear lymphadenopathy Management → oral acyclovir Investigations • Nucleic acid amplification test (NAAT) are recommended as the preferred diagnostic method for genital herpes. now regarded as the test of choice. PCR (a type of NAAT) : detects HSV RNA; identification of virus genotype • Western blot the gold standard for the detection of antibodies to HSV, but it is not commercially available. expensive, time consuming and requires skilled interpretation. high sensitivity
 have ability to discriminate between HSV-1 and HSV-2 antibodies. • Viral culture gold standard for definitive diagnosis; 100% specificity for HSV-1 or HSV-2 The culture should be taken from a fresh vesicle, either from skin or genitals. • Light microscopy findings on a Tzanck smear Detects multinucleated giant cells (nonspecific) Eosinophilic intranuclear Cowdry A inclusion bodies Unable to differentiate between HSV-1 and HSV-2, also commonly positive in VZV rarely used

now for diagnosis. can be performed when an urgent result is needed and no alternative test is immediately available Management • Antiviral treatment reduces the severity of episodes but is not curative. • gingivostomatitis: oral aciclovir, chlorhexidine mouthwash • cold sores: topical aciclovir although the evidence base for this is modest

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• genital herpes: oral aciclovir. Topical anaesthetic agents, e.g. 5% lidocaine (lignocaine) ointment Recommended regimens : Aciclovir 400 mg three times daily OR Valaciclovir 500 mg twice daily (for 5 days) Some patients with frequent exacerbations may benefit from longer term aciclovir more than six herpes episodes over the past 12 months →trial of suppressive therapy (aciclovir 400 mg BD for 12 months). Genital herpes in pregnant lady: Aciclovir is considered safe and well tolerated. If genital herpes is not recurrent and healed after a course of aciclovir: There is no need to continue suppressive therapy throughout the pregnancy. Restart acyclovir 400 mg TDS suppressive dose from week 36 to prevent active lesions being present at the time of delivery, where caesarean would definitely be needed. If there is a history of recurrent genital herpes → she should continue taking acyclovir 400 mg TDS until the end of the pregnancy If there are active lesions or prodromal symptoms at the time of delivery → A caesarean section should be considered Early treatment of herpes infections is essential to prevent complications because antiviral drugs only inhibit the virus during its replication phase

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Yellow fever • Type of viral haemorrhagic fever (also dengue fever, Lassa fever, Ebola). Aetiology • Pathogen: yellow fever virus (genus Flavivirus) • linear RNA virus • spread by Aedes mosquitos (primarily Aedes aegypti) • incubation period = 2 - 14 days Epidemiology • endemic in large parts of South America and Africa but not in Asia. Features • Most patients remain asymptomatic • In symptomatic patients: classic progression in three stages

1. Period of infection (3–4 days)

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 Sudden onset of fever (up to 41°C) Headaches, chills Nausea, vomiting Bradycardia may develop 2. Period of remission (up to 2 days) Easing of symptoms and decline in fever 3. Period of intoxication (only in ~15% of symptomatic patients) Hemorrhage Multiorgan dysfunction (e.g., acute kidney and liver failure) Nausea, (bloody) vomiting, abdominal pain, severe jaundice Zone 2 of the liver is most affected in Yellow fever. Yellow fever is suggested by:

1. Travel to endemic area (West Africa and Central America)
2. Fever, with initial resolution
3. Progression to jaundice and renal failure Investigations • Leukopenia • Thrombocytopenia, ↑ PTT • Signs of organ failure (acute liver failure, acute renal failure) • Virus detection PCR: the best test to rule out yellow fever infection is PCR ELISA • Liver biopsy Used

for definitive diagnosis (e.g., postmortem) Must not be done while the patient has an active yellow fever infection May show Councilman bodies Councilman bodies (inclusion bodies) may be seen in the hepatocytes For exam purposes Councilman bodies (eosinophilic inclusion in the liver on post mortem) are diagnostic of yellow fever, although they can occasionally be seen in other Viral Haemorrhagic Fevers such as Crimean Congo Haemorrhagic Fever, (but this is nosocomially spread) Treatment • Symptomatic treatment • No specific antiviral treatment is available Prevention • Yellow fever vaccine the vaccination is the only intervention which could prevent death . a live, attenuated vaccine that consists of the 17D strain of the virus, grown in hens' eggs. Administration A single dose is provides life-long protection administer at least 10 days before traveling to endemic area. Its use is contraindicated in: Under six months With previous confirmed anaphylactic reaction to the vaccine previous confirmed anaphylactic reaction to egg thymus disorder immunocompromised due to a congenital condition, disease process or treatment.

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Human immunodeficiency virus (HIV) Aetiology • Consists of the two species : HIV-1: most common species worldwide HIV-2: restricted almost completely to West Africa Pathophysiology • HIV attaches to the CD4 receptor on host cells with its gp120 glycoprotein (binding) • For fusion, CD4 receptor and a coreceptor (CCR5 in macrophages, and CCR5 or CXCR4 in T-cells) must be present. Viral entry into macrophages via CCR5 mainly occurs during the early stages of infection, while entry via CXCR4 occurs in later stages. Individuals without CCR5 receptors appear to be resistant to HIV, those patients either have a homozygous CCR5 mutation (substantial resistance) or a heterozygous CCR5 mutation (slower course). • gp120 is the HIV glycoprotein that can cross the placenta and infect the fetus. • The lymph nodes are the organs in which HIV replicates during the latent phase. Associations • Epstein-Barr virus reactivation, leading to B-cell lymphoma, typically occurs in AIDS patients with a CD4+ cell count less than 100/mm3. Routes of transmission • Sexual: responsible for ~80% of infections worldwide • Parenteral transmission • Needle sharing: → 0.67% • Vertical transmission: from mother to child during childbirth (~5–15%) • Features • In early HIV infection, patients are often asymptomatic. • Acute HIV infection (acute retroviral syndrome) (ARS) Typically occurs 2-12 weeks after infection Fever, Fatigue, Myalgia and arthralgia Generalized nontender lymphadenopathy Generalized rash Gastrointestinal symptoms (nausea, diarrhea, weight loss) Oropharyngeal symptoms (sore throat, ulcerations, painful swallowing) • Clinical latency and AIDS Clinical latency: Infected individuals may still be asymptomatic. Non-AIDS-defining conditions (common when CD4+ count is below 500 cells/mm3) Generalized lymphadenopathy Chronic diarrhea (> 1 month) Localized opportunistic infections Oral candidiasis: creamy, white patches on the mucous membranes of the mouth that can be scraped off Oral hairy leukoplakia: lesions that cannot be scraped off located mainly on the lateral borders of the tongue; triggered by Epstein-Barr virus HPV-related: squamous cell carcinoma of the anus (common in men who have sex with men) or cervix molluscum contagiosum, warts; shingles AIDS-defining conditions Kaposi sarcoma (typically

occurs at CD4 count < 500)

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 Mycobacterial infections (e.g, TB) Progressive multifocal leukoencephalopathy (typically occurs at CD4 count < 200) Disseminated or extrapulmonary coccidioidomycosis (occurs at CD4 count < 250) Pneumocystis pneumonia (occurs at CD4 count < 200) Disseminated or extrapulmonary histoplasmosis (occurs at CD4 count < 150) Conditions occurs at CD4 count < 100 Cerebral toxoplasmosis Extrapulmonary cryptococcosis (especially cryptococcal meningitis) Esophageal candidiasis or pulmonary candidiasis Herpes simplex Esophagitis Primary CNS lymphoma Conditions occurs at CD4 count < 50 Disseminated and/or extrapulmonary Mycobacterium avium complex Cytomegalovirus infection WHO (World Health Organization) classification • Primary HIV infection: acute retroviral syndrome or asymptomatic • Clinical stage 1: persistent generalized lymphadenopathy (PGL) or asymptomatic • Clinical stage 2: e.g., unexplained moderate weight loss (< 10%), recurrent fungal/viral/bacterial infections • Clinical stage 3: e.g., unexplained severe weight loss (> 10%), unexplained chronic diarrhea (> 1 month), unexplained persistent fever (≥ 37.6°C intermittent or constant > 1 month), persistent/severe fungal/viral/bacterial infections , unexplained anemia (< 8 g/dL) and/or neutropenia (< 500 cells/mm3) and/or chronic thrombocytopenia (< 50,000/µL) for more than 1 month • Clinical stage 4: AIDS-defining conditions (e.g., Kaposi sarcoma, Pneumocystis pneumonia) Diagnosis • HIV-1/2 antigen/antibody combination immunoassay (Ag/Ab immunoassay) (ELISA) Target of detection: IgM and IgG antibody and p24 antigen Approximate time to positivity: 15 to 20 days after event If a very early infection is suspected (less than 2 weeks), advice for: Serial testing at 1 month and again at 3 months from the date of the possible exposure OR HIV RNA viral load test p24 is the capsid protein of HIV, coded for by the gag gene. If negative → No further testing is required (exclude HIV) If positive → confirm by HIV-1/2 differentiation immunoassay (differentiates HIV-1 antibodies from HIV-2 antibodies) Unlike oral candidiasis, esophageal candidiasis is an AIDS-defining condition.

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• HIV viral load test Made by PCR of peripheral blood for HIV RNA Target of detection: RNA Approximate time to positivity: 5 – 15 days In acute HIV the viral load is very high. • HIV-1/2 differentiation immunoassay Confirmatory test , indicated following a positive HIV-1/2 Ag/Ab immunoassay The differentiation assay is now the standard confirmatory test Determines whether it is HIV-1 or HIV-2 infection If both Ag/Ab immunoassay and differentiation immunoassay are positive → confirm diagnosis of HIV and determine as positive for HIV-1 antibodies, HIV-2 antibodies, or HIV antibodies, undifferentiated. If Ag/Ab immunoassay differentiation was positive but differentiation immunoassay is negative (non-reactive) → test for HIV-1 nucleic acid test (NAT). • HIV-1 nucleic acid test (NAT) A reactive HIV-1 NAT result and nonreactive HIV-1/HIV-2 antibody differentiation immunoassay result indicates laboratory evidence for acute HIV-1 infection. A negative HIV-1 NAT and nonreactive or indeterminate HIV-1/HIV-2

antibody differentiation immunoassay indicates a false-positive result on the initial immunoassay • Flow cytometry is the lab technique used to measure CD4 cell count Used to determine the level of immune suppression once an infection is confirmed. The most useful investigation in estimating the risk of developing an opportunistic infection A count lower than 200/mm3 generally indicates progression to AIDS. • The Centers for Disease Control (CDC) no longer recommends Western blot confirmatory testing for HIV. Treatment • Since late 2015, the World Health Organization (WHO) has recommended starting ART in every HIV-positive individual, regardless of CD4 count. • In hepatitis B co-infection Antiretrovirals that also have anti-HBV activity should be included in the regimen used to treat HIV. These include: Emtricitabine Lamivudine Tenofovir Discontinuation of drugs that have anti-HBV activity can lead to reactivation of HBV and cause serious hepatocellular damage. • In patients with renal impairment → avoid tenofovir and consider avoiding atazanavir.

Initiation of ART should be delayed in the setting of TB meningitis and cryptococcal meningitis because of the high risk of immune reconstitution syndrome Stopping NRTIs in patients with hepatitis B co-infection can lead to an acute worsening of their hepatitis!

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HIV and pregnancy Efavirenz is the only antiretroviral medication that is contraindicated in pregnancy (teratogenic) Epidemiology • In London the incidence may be as high as 0.4% of pregnant women. Factors which reduce vertical transmission (from 25-30% to 2%) • maternal antiretroviral therapy • mode of delivery (caesarean section) • neonatal antiretroviral therapy • infant feeding (bottle feeding) Screening • NICE guidelines recommend offering HIV screening to all pregnant women Treatment • The aim of treating HIV positive women during pregnancy is to minimise harm to both the mother and fetus, and to reduce the chance of vertical transmission. • Antiretroviral therapy all pregnant women should be offered antiretroviral therapy regardless of whether they were taking it previously if women are not currently taking antiretroviral therapy the RCOG recommend that it is commenced between 28 and 32 weeks of gestation and should be continued intrapartum. BHIVA recommend that antiretroviral therapy may be started at an earlier gestation depending upon the individual situation No routine dose alterations are recommended for ARVs during pregnancy if used at adult licensed doses. It is recommended that women conceiving on an effective anti-retroviral (ART) regimen should continue this even if it contains efavirenz or does not contain zidovudine. Exceptions are: (1) Protease inhibitor (PI) monotherapy should be intensified to include (depending on tolerability, resistance and prior antiretroviral history) one or more agents that cross the placenta. (2) The combination of stavudine and didanosine should not be prescribed in pregnancy. • Mode of delivery vaginal delivery is recommended if viral load is less than 50 copies/ml at 36 weeks, otherwise caesarian section is recommended zidovudine infusion should be started four hours before beginning the caesarean section • Neonatal antiretroviral therapy zidovudine is usually administered orally to the neonate if maternal viral load is <50 copies/ml. Otherwise triple ART should be used. Therapy should be continued for 46 weeks. • Infant feeding: in the UK all women should be advised not to breast feed

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HIV: anti-retrovirals Overview • Start HAART as soon as possible after diagnosis regardless CD4 count. • Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging Atripla® (efavirenz, tenofovir, emtricitabine) is an acceptable choice. Nucleoside analogue reverse transcriptase inhibitors (NRTI) (ine at the end) Emtricitabine causes hyperpigmentation of skin including palmar creases in 8% of black patients. • examples: zidovudine (AZT), lamivudine, stavudine, didanosine, zalcitabine • general NRTI side-effects: Peripheral neuropathy Mitochondrial toxicity →dilated cardiomyopathy NRTI →reduce vascular responsiveness to acetylcholine → endothelial dysfunction. Mitochondrial dysfunction induced by HAART →decreased myocardial contractility. This is because cardiac myocytes can utilise energy less well, leading to decreased ejection fraction and dilative cardiomyopathy. myocardial biopsy usually reveals mitochondria full of myelin, a sign of mitochondrial dysfunction. Withdrawal of zidovudine and substitution with an agent associated with less mitochondrial toxicity, coupled with appropriate treatment for heart failure with diuretics and ACE inhibition, usually resolves the problem, although HIV itself is decreasingly recognised as a cause of cardiomyopathy. • zidovudine: anaemia, myopathy, black nails most frequently causes anaemia, usually by bone marrow suppression and patients can become transfusion-dependent in severe cases.

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 Macrocytosis is a typical finding in patients on zidovudine and can be used as a parameter to monitor adherence to therapy. Other side-effects of zidovudine include: Myalgia, Myopathy, Myositis Elevated CK → a picture of rhabdomyolysis Pancytopenia, Lactic acidosis. Blue or black discolouration of the nails is a rare side-effect. May be misdiagnosed as cyanosis and melanoma. • Didanosine: pancreatitis (Didanosine and stavudine cause mitochondrial toxicity, hence peripheral neuropathy, pancreatitis and hyperlactataemia.) • NRTIs - in particular stavudine, didanosine and zidovudine - classically cause mitochondrial toxicity as an unwanted side effect. This can result in nausea, pancreatitis, lactic acidosis and lipoatrophy • Truvada →combination of two (Nucleoside analog reverse-transcriptase inhibitors (NRTIs) : tenofovir disoproxil and emtricitabine tenofovir may cause:

1. life-threatening liver damage
2. lactic acidosis
3. sudden worsen of hepatitis B after stopping tenofovir →lab tests regularly for several months after stop. • Abacavir: (the only NARTI which is not ended by (ine)) is a nucleoside reverse transcriptase inhibitor (NRTI). It is recommended by the British HIV Association (BHIVA) in association with lamivudine as an alternative to Truvada as part of

a HAART regime. Abacavir causes a hypersensitivity reaction in patients who are HLA-B5701 positive. However, this would occur within 1–2 months of starting treatment in the UK all patients would be tested prior to initiation. It is typified by nausea, vomiting, malaise and fever, with or without a rash. Non-nucleoside reverse transcriptase inhibitors (NNRTI) (vir in the middle) • Examples: nevirapine, delavirdine, efavirenz and etravirine. • Side-effects: P450 enzyme interaction (nevirapine induces), Skin rashes Rashes are common on starting treatment with nevirapine, occurring in ~15% of patients. Nevirapine can cause acute hepatitis and skin rash as a part of hypersensitive reaction this is the rationale for starting low-dose therapy with nevirapine in the first 2 weeks Serious side effects are more common in patients with relatively well preserved immune function. Acute hepatitis Efavirenz side effects more common →neuropsychiatry side effects. less common →Gynaecomastia Efavirenz is the most common HAART drug associated with gynecomastia.

Protease inhibitors (PI) (vir at the end) • Examples: indinavir, nelfinavir, ritonavir, saquinavir • Side-effects: diabetes, hyperlipidaemia, Hypertriglyceridaemia Buffalo hump, central obesity, P450 enzyme inhibition Lipodystrophy Indinavir: → renal stones, asymptomatic hyperbilirubinaemia Ritonavir: Potent inhibitor of the P450 system (3A4 inhibitor) Produces very significant elevations in plasma fluticasone (even an inhaled preparation). so, it increases the levels of rifampin. These levels are sufficient to suppress endogenous cortisol levels and produce Cushing's syndrome. Co-trimoxazole prophylaxis for Pneumocystis (PCP) is not necessary unless the CD4 count is below 200 Patient who have high viral load despite treatment: • Causes of treatment failure: poor adherence drug interactions or absorption issues primary resistance or superinfection with a new resistant strain. • All patients should have had a resistance test at baseline The most appropriate course of action is to arrange an urgent resistance test and manage the antiretrovirals accordingly with this result. Patient who have TB associated with HIV: • Efavirenz is used in combination with an NRTIs because it has little effect on the plasma levels of rifampin which is being used to treat the pulmonary tuberculosis. Preventing Opportunistic Infections in Patients With HIV • Initiation of Prophylaxis and Treatment Patients not taking ART who present with disseminated Mycobacterium avium complex (MAC) infection should be treated for the infection without ART for 2 weeks, and then started as soon as possible on ART while monitored closely for symptoms of the immune reconstitution inflammatory syndrome (IRIS). Severe IRIS has also been reported after early ART in the management of cryptococcal and tuberculous meningitis, and it has been suggested that such patients delay ART until 4-6 weeks after control of the opportunistic infection. Patients with CD4 counts of less than 50 cells/µL at presentation should be considered for cryptococcal antigen testing, among those diagnosed with cryptococcal meningitis, initial ART should be delayed at least 2 weeks into cryptococcal therapy and as long as 10 weeks. which must be treated initially with amphotericin and flucytosine. • CD4 counts are useful landmarks for initiation of antimicrobial prophylaxis: Less than 250 cells/µL - Coccidioidomycosis prophylaxis if seropositive in high-risk area

 Patients with a new positive immunoglobulin M (IgM) or IgG serologic test result who live in endemic areas and have a CD4 count of less than 250 cells/µL should receive fluconazole 400 mg PO daily Less than 200 cells/µL - PCP prophylaxis The preferred regimen is trimethoprim-sulfamethoxazole 1 double-strength tablet orally daily or 1 double-strength tablet orally 3 times weekly. Less than 150 cells/µL - Histoplasmosis prophylaxis if high-risk exposure Patients with a CD4 count of less than 150 cells/µL at high risk for exposure or who live in a hyperendemic area should receive itraconazole 200 mg PO daily Less than 100 cells/µL - Toxoplasmosis prophylaxis (if seropositive) Trimethoprim-sulfamethoxazole, one double-strength tablet orally once daily is preferred Less than 100 cells/µL - Penicilliosis prophylaxis if living in high-risk area Less than 50 cells/µL - MAC infection prophylaxis Patients with CD4 count of fewer than 50 cells/µL should be given azithromycin 1200 mg orally weekly after ruling out disseminated MAC infection on clinical assessment Alternatives include clarithromycin 500 mg orally twice daily or rifabutin 300 mg orally daily • Clinical Landmarks for Terminating Primary Prophylaxis Mycobacterium avium-intracellulare (MAI) infection prophylaxis: should be continued with antiretroviral therapy (ART) until the CD4 count exceeds 100 cells/µL for 3 months. P carinii pneumonia (PCP) and toxoplasmosis prophylaxis: should be continued until the CD4 count exceeds 200 cells/µL for 3 months. Histoplasmosis prophylaxis: can be discontinued when the CD4 count has exceeded 150 cells/µL for 6 months, coccidioidomycosis prophylaxis: can be discontinued when CD4 counts exceed 250 cells/µL for 6 months, penicilliosis prophylaxis: can be discontinued when CD4 counts exceed 100 cells/µL for 6 months.

HIV lipodystrophy (Antiretroviral-related lipodystrophy) • Lipodystrophy (loss of adipose tissue), lipoatrophy and alterations in serum lipid values have been observed in patients with human immunodeficiency virus (HIV) disease taking highly active antiretroviral therapy (HAART). • Consequences ↑serum lipid levels → premature coronary artery disease. Hypertriglyceridaemia → central fat deposition and insulin resistance (Antiretroviral insulin-resistance syndrome) there is some evidence that the insulin sensitisers (glitazones) may be effective in some patients

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• Causes Abnormalities of serum lipid levels are likely to be multifactorial in patients with HIV disease but appear much commoner in patients taking protease inhibitors. Isolated hypertriglyceridaemia can occur in HIV disease in the absence of protease inhibitors but extremely high serum triglycerides have been documented in some patients treated with these drugs. • Treatment Mild to moderate hyperlipidaemia → 1st line dietary modification and exercise Predominant hypercholesterolaemia or with a mixed picture →statin Caution must be exercised since some protease inhibitors interact with some statins due to metabolism by CYP3A4 pathway. Simvastatin is contraindicated in patients on protease inhibitors and plasma levels of atorvastatin are also greatly elevated in these patients. For this reason, pravastatin is usually the drug of choice. Pravastatin is preferred because its metabolism is not as dependent on the

CP450s as other agents in this group. Hypertriglyceridaemia →fenofibrate Switching therapy might be an option, to non-nucleoside reverse transcriptase inhibitors (NNRTIs) In women with lipoatrophy syndromes, oral estrogens should be avoided as they can exacerbate the hypertriglyceridemia and result in acute pancreatitis. Immune reconstitution syndrome • Due to activation of the immune system following HIV therapy against persisting antigen. • Typically occurs a few weeks after commencing anti-retroviral therapy in a patient with underlying tuberculosis. HIV: biliary and pancreatic disease • The most common cause of biliary disease in patients with HIV is sclerosing cholangitis due to infections such as CMV, Cryptosporidium and Microsporidia • Pancreatitis in the context of HIV infection may be secondary to anti-retroviral treatment (especially didanosine) or by opportunistic infections e.g. CMV

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