Tuberculosis is caused by mycobacterium tuberculosis – an acid fast bacilli which contains a high concentration of lipids in the cell wall, the infection occurs after inhalation of an infected droplet. Tuberculosis predisposing factors are age, malnutrition, alcoholism, immunodeficiency, and poor living conditions. Symptoms = chronic cough, fever, night sweats. Treatment – initial phase (2 months) – isoniazid, rifampicin, pyrazinamide and ethambutol. Continuation phase (4 months) – isoniazid, rifampicin. Monitoring = liver function test, renal function test and eye tests.

Bronchitis – involves the production of mucopurulent sputum instead of usual mucoid and is caused by H influenzae and S pneumoniae.

Antimicrobial use: Advantages of combination therapy = reduction in the likelihood of drug resistance, provide synergy, improved survival, wide spectrum. Disadvantages = interaction, cost, side effects, and different pharmacokinetics.

Viruses: are static structures so they have NO metabolic activity of their own and so they rely on the host biosynthetic machinery for protein synthesis. Viruses are not causes of spoilage. Viruses contain viral genome in a protein coat – either DNA or RNA. RNA viruses include HIV and influenza. DNA viruses include HepB and herpes simplex. Parasites include helminths and protozoa. Sulphonamides and trimethoprim inhibit folate synthetase and are inactive against anaerobes. Glycopeptides inhibit 

B lactam antibiotics like penicillin which kill actively growing and dormant bacteria, potentially bactericidal antibiotics like isoniazid and ethambutol which kill actively dividing bacteria, and also bacteriostatic antibiotics. Rifampicin blocks RNA polymerase and induces CYP450. Steroids reduce fibrosis (scarring) during healing.

C.difficile causes diarrhoea which can be treated using vancomycin. Diarrhoea can be caused by ciprofloxacin. Trimethoprim is used for UTIs. If a patient has shortness of breath – they may have pneumonia, but additional tests needed for diagnosis - chest x-ray, C-reactive protein, white blood count, urea and electrolytes, erythrocyte sedimentation rate. Other information needed = allergy status and details, if patient is pregnant, if the patient has had recent contact with animals, if the patient has travelled recently, if the cough is productive, antibiotics taken, full history, and investigations for infection = skin, blood, urine, faeces, X-ray. Monitor white cell count, C reactive protein, erythrocyte sedimentation rate. Sepsis can cause meningitis, UTI’s, chest infections, septic shock caused by hypotension and decreased tissue perfusion), metabolic changes like increased carbohydrate metabolism and changes in cytokine production, and also malnutrition. Monitor white cell count, C reactive protein, erythrocyte sedimentation rate. Sepsis can cause meningitis, UTI’s.

C Reactive Protein (CRP) is a useful indicator for acute inflammation.

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Treatment: sterilising antibiotics like rifampicin which kill actively growing and dormant bacteria, potentially bactericidal antibiotics like isoniazid and ethambutol which kill actively dividing bacteria, and also bacteriostatic antibiotics. Rifampicin blocks RNA polymerase and induces CYP450. Steroids reduce fibrosis (scarring) during healing.

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Protease inhibitors do not inhibit host enzymes like trypsin or pepsin and therefore there is reduced toxicity (1). The function of protease inhibitors is to prevent post-translational modification of viral proteins leading to the production of non-infectious virus particles (1). When HIV-1 protease inhibitors are used in combination with other agents they bring about a dramatic clinical improvement and reduction in HIV related deaths. So they are very effective in combination with other drugs (1). Resistance occurs due to mutations around the active site (1) resulting in reduced affinity for inhibitors (1). Side effects = lipodystrophy (1) which is abnormal distribution of body fat (characterised by peripheral lipoatrophy, fat accumulation within the abdomen, hypertriglyceridaemia and insulin resistance (1)), high blood sugar and development of diabetes, liver toxicity, blood tests that monitor liver function as well as cholesterol and triglyceride levels are routine in patients on protease inhibitor therapy (1), high blood pressure. A typical of protease inhibitors (1). Many protease inhibitors appear less active against HIV-2 protease (1). The length of the polypeptide enzyme structures which causes reduced binding and therefore higher concentrations of protease inhibitor are needed. Some protease inhibitors can be used against hepatitis C (1). Protease inhibitors example = Ritonavir, Amprenavir, Indinavir, Saquinavir.

- Interference with capsid maturation using maturation inhibitors: this is when the host cell newly constructed virus particles undergo a maturation process – a key step in viral replication. Maturation of HIV viruses, which occurs as they bud off from the infected cell, is triggered by the step from the Gag precursor to the major viral structural protein ‘p55’ Gag to individual, mature Gag proteins (1). When the capsid is assembled, it can cause the membrane to become defective and non-infectious. Current maturation inhibitors interfere with the proteolytic cleavage of the Gag precursor protein from processing between the two particular cleavage site. Maturation inhibitor examples = Bevirimat which is a cyclic guanosine (gag) protein processing inhibitor and acts more specifically at CA-SP1 cleavage site which is between Gag capsid (CA) and capsid (p24) sugars in clinical failures in vivo may occur due to polymorphisms in putative capsid protein cleavage sites preventing drug binding. Another example of a maturation inhibitor = PF-46396. Treatment of other viral infection considerations: 1. therapeutic index which is concept that refers to the relationship between toxic and therapeutic dose. It determines how safe or toxic a drug is. 2. Severity of disease.

**Herpes Virus** is treated using nucleoside analogue-1 like Idoxuridine which was synthesised in 1959. It replaces thymidine in growing DNA chains, and can still form chains as it possesses –OH groups at 5 and 3 positions on sugar. Treatment of organic base prevents binding to complementary base on DNA. It is too toxic to be used systemically, it cannot kill latent viruses and it only prevents replication. Nucleoside analogue-2 = aciclovir (acycloguanosine). Aciiclovir (Zovirax) is a substituted guanine derivative. It lacks an –OH group at position 3 on the sugar so cannot accommodate chain elongation. Aciiclovir is inactive and must be phosphorylated to form the nucleoside triphosphate in order to be used by DNA polymerase. Aciiclovir is very selective low in cytotoxicity. Nucleoside isolated from a Caribbean sponge – cryptothelya crypta are the basis for synthesis of aciclovir. Aciiclovir differs from previous nucleoside analogues in containing only a partial nucleoside structure - the sugar ring is replaced by an open chain structure. Activation of aciclovir: In the virus-infected cells aciclovir is phosphorylated by the viral enzyme thymidine kinase to form aciclovir monophosphate. Subsequent phosphorylation to di- and tri- phosphates is carried out by cellular kinases. In non-infected cells thymidine kinase does NOT exist and so aciclovir is not phosphorylated and remains inactive. Uses of aciclovir: used in treatment of herpes simplex infections of the skin and mucous membranes: HSV types 1 and 2, herpes simplex keratitis, Varicella Zoster (chicken pox and shingles). Aciclovir can be given orally, topically or IV infusion. Aciclovir is poorly water soluble and has poor bioavailability requiring IV administration to achieve high concentrations. pH of aciclovir solution is high (pH 11) and may lead to irritation at the site of infusion and because it is very insoluble absorption by mouth is poor and so high doses need to be administered. Valaciclovir is an esterified version of aciclovir and therefore has greater oral bioavailability. Famciclovir is also an oral produg which is converted by first pass metabolism to the antiviral drug penciclovir. Upon intracellular uptake, penciclovir is monophosphorylated by thymidine kinase and then converted to penciclovir triphosphate by cellular enzymes. Penciclovir triphosphate inhibits DNA polymerase of viruses but has no effect on cellular DNA polymerase. Penciclovir triphosphate has a lower affinity for viral DNA polymerase but a longer intracellular half life. Development of resistance: the virus may become thymidine kinase negative and so the drug will not become inactivated, the thymidine kinase may be altered in such a way that it does NOT activate aciclovir, the viral DNA polymerase may be altered so that it does not recognise the aciclovir triphosphate. Aciiclovir is most effect against herpes simplex type 1. Nucleoside analogue-3: Ganciclovir is a nucleoside analogue of guanosine. Ganciclovir is phosphorylated to ganciclovir monophosphate by virus encoded thymidine kinase. The di- and tri-phosphates are produced by the actions of cellular enzymes. It is a more efficient substrate than aciclovir for HSV1 thymidine kinase so more ganciclovir triphosphate is produced compared to aciclovir triphosphate. Ganciclovir mode of action: ganciclovir triphosphate slows viral DNA replication however, short subgenomic