Unit 1

What is the natural history for HIV - Immunity compromising parasite that causes AIDS(o-ccurs when immune system fails, too few CD4, opportunistic infections by pathogens that are usually not harmful), retroviruses that make DNA in host - Has geographically distributed infection patterns that show adaption and diversity - Across the world it is number 4 cause of death, 84M infections 40M deaths (covid is 600M + 6M), most prev in sub-Saharan Africa (23.5M) it decreases away from the eq. - The pattern since 1990s has been to increase then level off recently o In south Africa the life expectancy at birth decreased to levels unseen since 1960s (n shape), number of people newly infected each year has been decreasing esp since 200s as we started to understand it

Mode of transmission is region dependent - Likely mode of transmission is mainly hetero-sexual sex or injection in indo, kenya, Russia but MM sex in US and canada (hetero in uk!)

We have become complacent - Huge increase in infections in MM in USA in 84, shot down in 1987 with drugs but increasing slowly as we are complacent

Unit 1 (cont)

How HIV infects a cell 1. HIV virion has RNA genome with integrase, protease, RT inside, gp41 anchor protein with gp120 surface protein 2. Binds to CD4, coreceptor,CCR5 on human cell and fuses 3. RT creates DNA which is spliced into host by integrase, making it transcribe HIV mRNA and create new HIV proteins which assemble and bud off, then mature into new virion

Immune system response - Dendrite captures virus and activates naïve helper T, these produce effector helper T (some also become memory helper T cells) - Effectors stimulate B cells which make antibodies that inactivate the virus, also activate killer T which destroy hosts who have the virus - But macrop-hage, effectors and memory Ts have CD4 and CCR5 which makes them targets for HIV

HIV load - Virions Acute(0-12): sharp increase then decrease as immune fights Chronic(1yr-7): levels off as they infect t cells AIDs: sharp increase again - CD4 Tcells, acute: sharp decrease as they fight chronic:i-ncrease in blood at start but then slowly goes down until it hits AIDS:200cells/mm3

Affects on body - Chronic infection damaged lymp leading to less T, HIV depletes CD4+ T in gut damaging it, allows bacteria into blood, bacteria in blood induces immune system which causes T cell prolif, giving HIV more cells to target (it does best in activated CD4+ Ts)

Unit 1 (cont)

Why did single drug therapies fail AZT - Developed within 5 years, very promising, AZT is added instead of Thymine DNA to DNA by RT, less likely in mutants with RT errors, will add DNA Thymie with amide which stops the chain - Population inside will evolve within about 6 months, need to keep increasing the concentration, new RT will add it but then correct the mistake and remove it (likely still added though) - Natural selection occurs as there is a population inside an individual with mutations, when the population changes (AZT intro), resistant virions become the most fit (before they were less fit) could go back, natural selection is enviro and reversible o Changed to genetic makeup in HIV pop over time led to increased drug resistance, virions with heritable traits conferred enhanced fitness ✉ greater proportion in HIV populations

HAART - Highly active antiretro-viral therapy (3+ drugs), increased survival, takes longer to evolve resistance to multiple drugs - Risk of evolving HIV resistance increases when you have done 80-90 prescriptions, many stop here because side effect is so bad ✉ resistant populations

Unit 1 (cont)

Where and when did HIV originate - HIV can evolve in one person and then an ancestor goes to the next patient, new enviro=new evo, we can build an accurate diagram with some parts! - HIV-1 was transfected from chimps to people many times HIV-2 was from monkeys o HIV2 is not as transmissible or fatal and didn't cause the epidemic, group M HIV1 is the most prevalent strain and our species had no T to deal with it - HIV evolves rapidly which makes vax hard - To estimate the time we had to guess the starting point, used unrooted phenogram, genetic differences and linear regression (molecular clock) 159 strains and do pairwise comparison, estimate divergence from common ancestor and extrapolate (back to 1914-1915)

unit 2