HIV – Key Notes

Virology	HIV-1 is a nine-gene RNA retrovirus, of the lentivirus genus. It causes the acquired immune deficiency syndrome (AIDS) The virus carries 2 RNA copies of its genome within virus particle. The genome is enveloped in a lipid membrane derived from an infected cell. This aids it to evade the host immune system. It contains the enzyme viral reverse transcriptase, which converts them to 1 DNA copy in the cytoplasm of the infected cell This copy is integrated (using integrase enzymes) into the host cell DNA and uses the cell's genetic machinery to make new virus Protease enzymes are involved in the assembly of the viral core. It infects cells of the immune system – CD4+ lymphocytes, macrophages and brain microglia Transport is from entry at mucosa to lymph nodes, where acute lymphocyte activation is followed by high levels of virus replication, cell destruction and turnover Unlike many other viruses, it can infect cells that are not dividing But takes years for CD4+ cell count to fall to threshold for symptomatic immunodeficiency
Epidemiology	Approximately 38 million people estimated to be living with AIDS worldwide (2006) Approximately 25 million people estimated to have died from AIDS worldwide 40% women, of whom 70% live in sub-Saharan Africa Elsewhere, 1/3 infections from intravenous drug use, esp in E Europe & southeast Asia
Groups at special risk	Patients receiving blood transfusions Haemophilia patients Intravenous drug users (IVDUs) People with tattoos Needlestick injuries (particularly in healthcare workers, refuse collectors picking up discarded needles, and friends and children of people using needles, such as IVDUs) Heterosexual transmission

Sexual transmission risk increased with episodic recreational drug or alcohol use
Multiple sexual partners, prostitutes, rape victims, women finding difficulty resisting promiscuous partners (esp demanding "dry" sex)
Male homosexuals
Children of HIV positive mothers
Prisoners

Natural History

HIV infection

Highest levels of viraemia in acute infection, advanced disease and transmission may be facilitated in presence of other sexually transmitted diseases (gonorrhoea, genital herpes).

There are various different strains of HIV, and a person already infected with one strain has the potential to acquire another strain if protection is not used.

A person who is infected will remain HIV antibody negative for the first three months after infection

Seroconversion illness

- Typically 10-14 days after infection
- Rash, fever, malaise, sore throat, generalised lymphadenopathy, fatigue, myalgia
- Additionally oral and /or genital ulceration may occur; also meningitis, encephalitis, Guillain-Barré syndrome.
- Symptoms last 1-2 weeks

Duration of time to develop to AIDS

- Some patients can be HIV-positive for years without progression to AIDS.

AIDS

Without treatment, AIDS is a condition that can be quickly fatal. However, because of HAART, AIDS for some people is a chronic condition that they can live for years with.

It is, however, important to recall that life on toxic long-term medication is not a picnic, and there is a danger for many of risk compensation (a tendency to ignore the risks of contracting AIDS because of the misguided impression that it is easily treated if one gets it).

Special features for intravenous drug users

Mortality was high before needle exchanges came in. In a small study in Dublin, 53 (65%) of a cohort of 82 GP patients aged 15-24 contracted HIV between 1985 & 1994, and 18 (22%) died.

Needle exchanges have been shown to be effective in reducing the spread of HIV among IVDUs.

Methadone maintenance associated with reduction in risk of progression of HIV infection to AIDS

	Years of follow-up		
	1	2	3
Persistent injecting	11	36	60
Methadone maintenance	2	11	29
Proportion (%) of drug users progressing to AIDS (BMJ 1990; **301**:1362)			

Interaction of certain antiretroviral medications with methadone / buprenorphine (see Table below)

Amphetamines may interact fatally with HIV medications: 1 case report of patient on stavudine, saquinavir and ritonavir who died after injecting methamphetamine; 2 died after taking MDMA on ritonavir-containing regimens.

IVDUs do not always take antiretroviral therapy in a consistent way. Some efficacy in IVDUs improving adherence to HAART reported when medication supervised rather than unsupervised or if voucher-based contingency management programme used.

Clinical presentation

HIV infection

Asymptomatic
Picked up on routine testing of patient in high-risk group, insurance testing

AIDS

Episode of an AIDS related or defining illness or condition

- Kaposi's sarcoma
- *Pneumocystis carinii* pneumonia
- CMV retinitis
- Disseminated histoplasmosis

Significant weight loss
Neuropsychological dysfunction

	Illnesses complicating or resulting from AIDS (see Table below)
Investigation and diagnosis	HIV testing CD4+ testing for staging and monitoring
Treatment	Prevention Highly-active antiretroviral therapy (HAART) Treatment of physical and psychological sequelae of AIDS Advice about safe sex Specialist drug addiction treatment service (smoking, stimulants [e.g., methamphetamine] intravenous drug use) Easy access to sexual health services (sexually transmitted diseases other than HIV) Specialist dietary advice Specialist dental treatment Specialist foot treatment, especially chiropody Respite admissions Emotional support for patient, partners and family Support for physical and social problems (lack of job, income, need for carer and supplies at advanced stage), both formal (specialist social workers) and informal
Prevention	*Primary prevention* Education and reduction of number of sexual partners Fidelity in monogamous relationships Condom use (male and female), microbicide Circumcision Needle exchanges – have been shown to be effective in reducing the spread of HIV in intravenous drug users Treat associated sexually transmitted diseases vigorously Treat vaginal infections (e.g. trichomonas) vigorously *Secondary prevention* Intrapartum nevirapine (1 dose) or Caesarian section can reduce mother-to-child transmission at the time of delivery. Avoid breast feeding if supply of replacement feeding is cheap and safe. Methadone maintenance in IVDUs Postexposure prophylaxis with antiretroviral therapy after occupational (needlestick injury) or non-occupational (rape, sexual abuse) exposure (‘golden hour’)

Counselling pre-testing

There are five main components of pre-test discussion. These are:

1. Ensuring the individual understands the nature of HIV infection; provision of information about HIV transmission and risk reduction.
2. A discussion of risk activities the individual may have been involved in with respect to HIV infection including the date of the last risk activity and the perception of the need for a test.
3. Discussion of the benefits and difficulties to the individual, his or her family and associates of having a test and knowing the result whether positive or negative.
4. Providing details of the test and how the result will be provided.
5. Obtaining an informed decision about whether or not to proceed with the test.

Counselling post-testing

The aims of post-test counselling are to:

- Address immediate concerns and provide support for those who are positive.
- Provide information on the prevention of HIV transmission for both those who are diagnosed as HIV positive and those HIV negative.

If the individual is diagnosed as HIV positive the counsellor should:

- Address the patient's immediate reactions.
- Refer for specialist management, including treatment where appropriate.
- Give details of support services.
- Offer follow up appointments and ongoing support which may include addressing issues concerned with legal matters and support for carers and partners

(doh, http://www.advisorybodies.doh.gov.uk/eaga/guidelineshivtestdiscuss.htm)

Drug Therapy

Highly active antiretroviral therapy (HAART)
Prophylactic therapy

- Co-trimoxazole for PCP

HAART – Different classes of drugs

Protease inhibitors

Indinavir
Ritonavir
Saquinavir
Nelfinavir
Amprenavir
Lopinavir
Atazanavir
Tipranavir
Darunavir

Nucleoside reverse transcriptase inhibitors

Zidovudine
Didanosine
Stavudine
Zalcitabine
Abacavir
Lamivudine
Emtricitavine
Tenofovir

Fusion inhibitor

Enfuvirtide

Non-Nucleoside reverse transcriptase inhibitors

Nevirapine
Delavirdine
Efavirenz
Etravirine
Rilpivirine

CCR5 antagonists

Maraviroc

Integrase inhibitors

Raltegravir
Elvitegravir (in trial)

Combination drugs

Epzicom (abacavir, lamivudine)
Combivir (zidovudine, lamivudine)
Truvada (tenofovir, emtricitabine)
Trizavir (abacavir, lamivudine, zidovudine)
Atripla (efavirenz, tenofovir, emtricitabine)

Drug Classes in Trial

Attachment inhibitors
Maturation inhibitors

Survival has increased greatly as combinations of drugs have been used.

Major side effects
Lipoatrophy
Lipodsytrophy
Hyperglycaemia
Hypercholesterolaemia
Lactic acidosis
Pancreatitis

Monitoring of progress
Monitoring of CD4+ cell counts indicate the status of the disease progression, response to treatment and treatment resistance

Psychological Support

Issues for people treating people with AIDS to bear in mind

1. Personal emotional responses to AIDS

Avoidant coping, drug use
Depression; grief reactions (loss of healthy body image, loss of own life (potential), death of friends / others who have AIDS); coming to terms with how they got infected and the person who infected them, especially if virus obtained traumatically such as by rape.
Incorporation of AIDS as part of own identity into self over time
Coping with getting progressively ill
Coping with disability
Coping with new limitations and responsibilities (e.g, whether to prioritise own sexual needs or prioritise not passing virus on to a partner). Development of sense that happiness is for others, not the patient. Also, poverty may lead to sense of desperation and subsequent casual sex for money
Coping with stabilisation of AIDS and removal of the imminent threat of death
Coping when HAART fails

2. Coping with the outside world

Dealing with close relationships, which may be altered in the light of new information (close people may reject following disclosure of HIV, of homosexual orientation, of proximity to death etc)
Dealing with normal life stresses when increasingly unable to meet them
Coping with stigma (rejection, disclosure concerns, stereotyping, protective silence, feeling "other", victim of verbal or physical abuse, assault) for being gay, HIV +ve,
And doing so by withdrawal, joining support groups, seeking counseling, praying, not disclosing HIV status

3. Psychological factors relating to adherence to medication

Associated with adherence: Conscientiousness; ability to tolerate feelings of distress; positive attitude to antiretrovirals; higher self-efficacy for taking antiretrovirals as required; sense of responsibility to protect others from HIV; having informal care (instrumental or emotional support, peer support / buddy programmes); good relation with the physician; spirituality

Not helpful for adherence: depression, sharing injection equipment, depressive symptoms; living alone, homelessness, social discomfort in taking HAART; worry about being able to afford treatment.

4. Support for caregivers

Significant others / family / children / parents of adult ill people (grandparent support) / friends
Professional carers (nurses, doctors, social workers)
Associated carers (buddies)

Meaning in caring, bereavement & HIV, acknowledging and getting support for distress, growth, humor, support, rest and time out to reduce risk of burnout, spirituality are helpful in coping

Crisis after the death of the patient, as crisis of personal meaning / sense of redundancy for the carer

Prognosis	When first identified, 75% of the first 168 cases in the UK were dead at 28 months (2 years 4 months) (Marasca & McEvoy. *BMJ* 1986;292:1727-9) Currently survival significantly improved by HAART Prognosis worse when co-infection with Hepatitis C or TB
Public Health measures	Education Advertisements Attitudinal change Promote sexual abstinence, fidelity and condom use (ABC = Abstinence, Behaviour Change, Condoms) Promote attitudes of greater respect for women Reduce stigma against people who are HIV +ve or who have AIDS
User Groups	Terrence Higgins Trust National AIDS Manual

Mouth Dental abscess / caries periodontal breakdown linear gingival erythema necrotising ulcerative gingivitis necrotising ulcerative periodontitis Oral candidiasis Oral herpes simplex Hairy oral leucoplakia	*Urogenital/ perineal* Genital and perianal infections • Candida • herpes simplex • human papilloma virus (HPV) • Syphilis • Gonorrhoea Cervical dysplasia Cervical cancer (both from HPV and other causes) Anal cancer (both from HPV and other causes)	*Skin* Seborrhoeic dermatitis Tinea cruris Tinea pedis Pityriasis versicolor Impetigo Acneiform folliculitis Molluscum contagiosum Kaposi's sarcoma
Chest *Pneumocystis carinii* pneumonia *Pneumocystis jiroveci* pneumonia Tuberculosis Lung cancer	*Neurological* HIV encephalopathy AIDS dementia AIDS-related encephalopathy • Toxoplasmosis • CMV Neurosyphilis Progressive multifocal leucoencephalopathy	*Infections* CMV Cryptococcosis Toxoplasmosis Mycobacterium avium complex
Gastrointestinal Gastroenteritis, diarrhoea from Cryptosporidium spp, Isospora belli Lactose intolerance GI cancers	*Psychiatric* Fatigue Depressed mood (both biologic and psychologic causation) AIDS related hypomania Suicidality	*Other* Anaemia Thrombocytopenia Non-Hodgkin's lymphoma Osteopenia

Table: Some physical and psychological complications of AIDS

	Effect of HAART on opiate		**Effect of opiate on HAART**	
	Methadone	**Buprenorphine**	**Methadone**	**Buprenorphine**
Abacavir	↑Clearance	-	↑time to peak concentration, ↓ peak	-
Atazanavir	No change	Concentration increased	Lower trough with SU or opiate	Lower trough with SU or opiate
Atazanavir / ritonavir	-	Concentration increased	-	No effect
Delavirdine	↓Clearance, ↑t1/2β, ↑AUC (ie risk of methadone toxicity)	Statistically, but not clinically, significant prolongation of QTc interval, particularly as inhibits CYP3A4	No effect	-
Didanosine	No effect	-	↓AUC by 60%	-
Efavirenz	↓ methadone, may induce withdrawal requiring a dose adjustment (after 8days)	↓buprenorphine; Statistically, but not clinically, significant prolongation of QTc interval	-	-
Fosamprenavir	↓13%	?↑	-	-
Indinavir	No effect	?↑	-	-
Lopinavir	-	-	Lower trough with SU or opiate	Lower trough with SU or opiate
Lopinavir / ritonavir	No change	Statistically, but not clinically, significant prolongation of QTc interval	-	-
Nelfinavir	Reduced trough. Some say that can cause withdrawal, others that no adjustment to dose needed	Statistically, but not clinically, significant prolongation of QTc interval	-	-
Nevirapine	↓ 20mg/day and may induce withdrawal	?↓	-	-

	Effect of HAART on opiate		**Effect of opiate on HAART**	
	Methadone	**Buprenorphine**	**Methadone**	**Buprenorphine**
Ritonavir	-	Statistically, but not clinically, significant prolongation of QTc interval, particularly as inhibits CYP3A4	-	-
Ritonavir	Can cause withdrawal	-	-	-
Ritonavir / saquinavir	Can cause 40% decrease in total methadone, but mainly the inactive S-methadone isomer, so no dose adjustment necessary	-	-	-
Saquinavir	↓34%	?↑	-	-
Stavudine	No effect	-	↓AUC by 25%	-
Tenofovir	No effect	-	-	-
Tipranavir	↓50%	?↑	-	-
Zidovudine	No effect	-	↑AUC by 40%. May induce toxicity	No effect

Table: Interactions between antiretroviral drugs and drugs used for opiate substitution therapy in the treatment of heroin addiction