

Module 9

Management of Coinfections in HIV-Positive Injecting Drug Users

Treatment and Care for
HIV-Positive Injecting Drug Users



Module 9

Management of coinfections in HIV-positive injecting drug users

Participant Manual

2007



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For inquiries, contact The Public Affairs Office, The ASEAN Secretariat, 70A Jalan Sisingamangaraja, Jakarta 12110, Indonesia, Phone: (62 21) 724-3372, 726-2991, Fax: (62 21) 739-8234, 724-3504. E-mail: public@aseansec.org. General information on ASEAN appears on-line at the ASEAN Website: www.aseansec.org.

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Copies may be requested from:

The ASEAN Secretariat, 70A, Jl. Sisingamangaraja, Jakarta 12110, Indonesia. e-mail: public@aseansec.org

and

Family Health International, Asia/Pacific Regional Office, 19th Floor, Tower 3, Sindhorn Building, 130–132 Wireless Road, Lumpini, Phatumwan, Bangkok 10330, Thailand, e-mail: sunee@fhibkk.org

and

HIV Unit, Department of Communicable Diseases, World Health Organization, Regional Office for South-East Asia, Indraprastha Estate, Mahatma Gandhi Marg, New Delhi-110 002, India, e-mail: hiv@searo.who.int

Module 1: Drug use and HIV in Asia: participant manual

Module 2: Comprehensive services for injecting drug users – participant manual

Module 3: Initial patient assessment – participant manual

Module 4: Managing opioid dependence – participant manual

Module 5: Managing non-opioid drug dependence – participant manual

Module 6: Managing ART in injecting drug users – participant manual

Module 7: Adherence counselling for injecting drug users – participant manual

Module 8: Drug interactions – participant manual

Module 10: Managing pain in HIV-infected injecting drug users – participant manual

Module 11: Psychiatric illness, psychosocial care and sexual health – participant manual

Module 12: Continuing medical education – participant manual

Trainer manual: Treatment and care for HIV-positive injecting drug users

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Abbreviations and acronyms

3TC	lamivudine
ABC	abacavir
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase (liver enzyme)
ART	antiretroviral therapy
ARV	antiretroviral
ASEAN	Association of Southeast Asian Nations
AST	aspartate aminotransferase (liver enzyme)
AZT	zidovudine (also ZDV)
CBC	complete blood count
CCC	comprehensive continuum of care
CDC	Centers for Disease Control and Prevention (US Government)
CNS	central nervous system
CPT	co-trimoxazole preventive treatment
CTX	co-trimoxazole
d4T	stavudine
DNA	deoxyribonucleic acid
DOTS	directly observed treatment, short course
EFV	efavirenz
ESLD	end-stage liver disease
ETR	end-of-treatment response
EVR	early virological response
FHI	Family Health International
FTC	emtricitabine
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
HBcAb	hepatitis B core antibody
HBeAb	hepatitis B e antibody
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular cancer
HCV	hepatitis C virus

HEENT	head eye ear nose and throat
HIV	human immunodeficiency virus
IDUs	injecting drug users
IFN	interferon
IRIS	immune reconstitution inflammatory syndrome
LFT	liver function tests
MAC	<i>Mycobacterium avium</i> complex
NGO	nongovernmental organization
NNRTI	non-nucleoside reverse transcriptase inhibitors
NR	non-responder
NRTI	nucleoside reverse transcriptase inhibitors
NSAID	non-steroidal anti-inflammatory drug
NVP	nevirapine
OI	opportunistic infection
OST	opioid substitution therapy
PCP	<i>Pneumocystis jiroveci</i> pneumonia
PEG-IFN	pegylated interferon
PI	protease inhibitor
PLWHA	people living with HIV and AIDS
RBV	ribavirin
RCT	randomized control trial
RHZE	TB drug treatment regimen involving 4 drugs (H=isoniazid, R=rifampicin, E=ethambutol, Z=pyrazinamide)
RNA	ribonucleic acid
SS	sputum smear
SSRI	selective serotonin reuptake inhibitor
SVR	sustained virological response
TB	tuberculosis
TDF	tenofovir
TNP-plus	Thai Network for People Living with HIV/AIDS
TST	tuberculin skin test
ULN	upper limit of normal
USAID	United States Agency for International Development
VCT	voluntary counselling and testing
VL	viral load
WCC	white cell count
WHO	World Health Organization
ZDV	zidovudine (also AZT)

OVERVIEW



Objectives:

By the end of the session the participants will:

- Understand the epidemiology of viral hepatitis/HIV coinfection
- Understand the influence of viral hepatitis on progression of HIV
- Understand the influence of HIV on progression of viral hepatitis
- Understand the approach to HCV and HBV treatment in the context of HIV infection
- Understand the approach to HIV treatment in the context of viral hepatitis, including how to choose an appropriate ART regimen and monitor liver function
- Understand the importance of preventing bloodborne virus transmission in coinfection
- Understand the limitations of hepatitis management in resource-limited settings



Time to complete session:

1 hour 45 minutes



Session content:

Consider both HCV/HIV and HBV/HIV coinfection:

- Epidemiology
- Natural history
- Effect of HCV on HIV progression
- Effect of HIV on HCV progression
- Treatment of HCV in HIV coinfection
- Treatment of HIV in HCV coinfection
- Summary



Training materials:

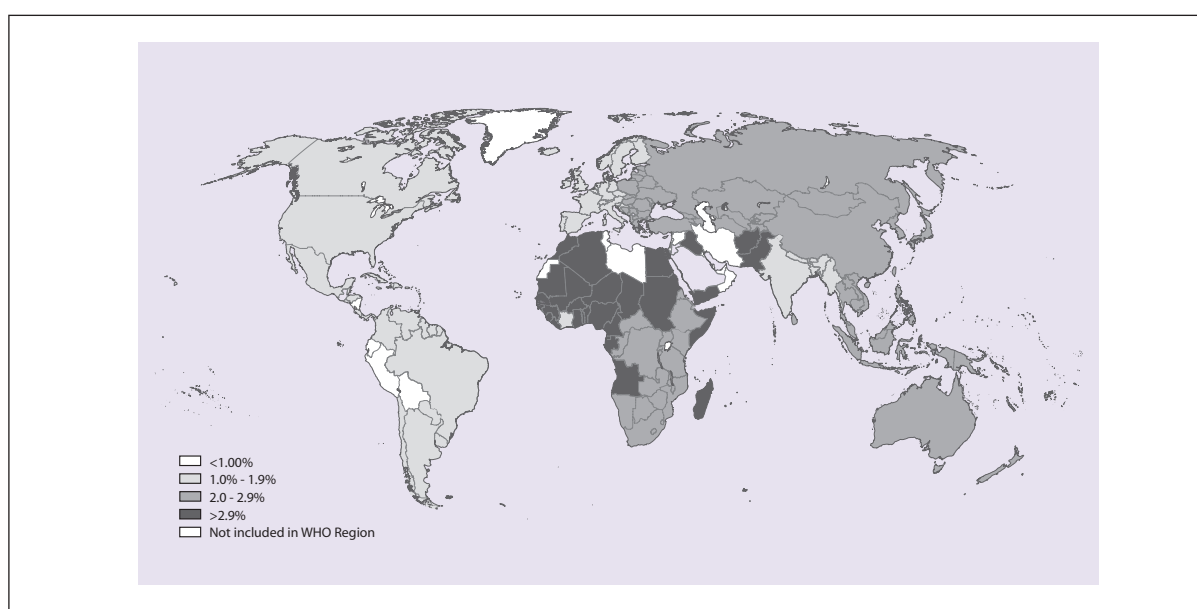
- PowerPoint presentation 9.1: HIV/HCV and HIV/HBV coinfections in HIV-infected IDUs
- Sub-module 9.1: HIV/HCV and HIV/HBV coinfections

HEPATITIS C COINFECTION

Epidemiology

There are 170 million individuals living with hepatitis C in the world. Most are from developing countries. There are a number of reasons for this which include unsterile medical injections, transfusions, cultural practices where blood is potentially exchanged between individuals, and injecting drug use. The prevalence by country is shown in Figure 1:

Figure 1. Prevalence of hepatitis C across the world, 2005



Source: Shepard CW, Finelli L, Alter MJ. *Lancet Infectious Diseases*, 2005

WHO Region	Total population (millions)	HCV prevalence (%)	Infected population (millions)	Number of countries by WHO Region where data are not available
Africa	602	5.3	31.9	12
Americas	785	1.7	13.1	7
Eastern Mediterranean	466	4.6	21.3	7
Europe	858	1.03	8.98	19
South-East Asia	1500	2.15	32.3	3
Western Pacific	1600	3.9	62.2	11
Total	5811	3.1	169.7	59

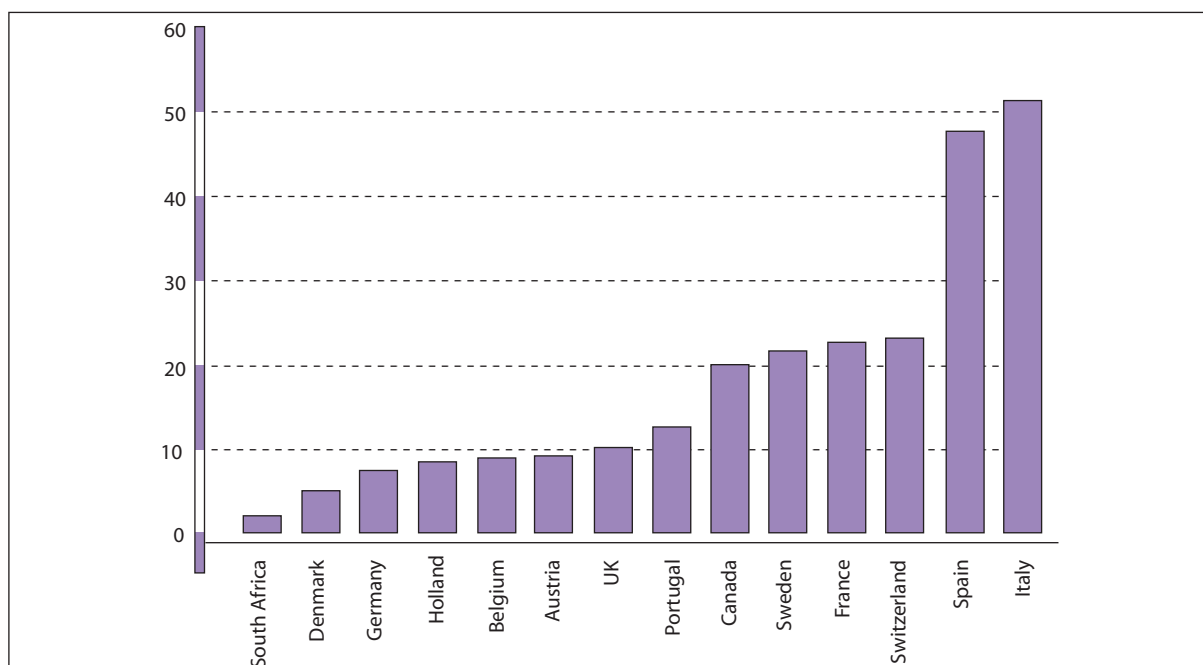
Source: Shepard CW, Finelli L, Alter MJ. *Lancet Infectious Diseases*, 2005

Although injecting drug use is a very common way of acquiring HCV, the proportion of HCV cases attributable to injecting drug use is lower in developing than developed countries. Screening of blood and blood products for HCV is an effective way to reduce transmission. This was first introduced in the late 1980s in Australia, Europe and the USA, but is now common in many countries. The country with the highest population prevalence of HCV is Egypt, a consequence of unsterile injections during a schistosomiasis treatment programme in the second half of the last century.

Within IDU populations, sharing of contaminated injecting equipment such as needles and syringes is the most common mode of HCV acquisition. Sharing of other equipment such as spoons and filters has also been associated with the transmission of HCV, though this is less common. HCV appears easier to transmit than HIV, and therefore the prevalence of HCV in an injecting drug user (IDU) population is often much higher than the HIV prevalence. HCV is difficult to transmit by unprotected sexual intercourse, though recent studies suggest that traumatic sexual practices are associated with HCV transmission.

The epidemiology of HCV/HIV coinfection is less well understood. Generally speaking, this coinfection, by the nature of the shared transmission routes, is transmitted by injecting drug use; however, transmission can also be sexual. Thus, coinfection is more common in IDUs than in the general population. HCV is more difficult to clear spontaneously in the presence of HIV; therefore, HIV-positive IDUs are much more likely to have HCV than their HIV-negative counterparts. In a number of countries in Asia, the prevalence of HIV/HCV coinfection among HIV-positive IDUs is >95% (parts of China, Thailand, Viet Nam). By contrast, most HIV-positive individuals are not HCV-positive in those countries when injecting drug use is not a major transmission route for HIV (see Figure 2; note Italy and Spain have a greater proportion of HIV infection attributable to injecting drug use).

Figure 2. Prevalence of HCV coinfection in HIV-positive individuals by country: CAESAR study



Source: Amin J et al. *HIV Medicine*, 2004.

The virus

Hepatitis C was formerly known as non-A non-B hepatitis. It was named hepatitis C in 1989 when the virus was discovered. It is a member of the Flaviviridae family. Other viruses of this family include Japanese encephalitis, dengue and West Nile virus. It is unrelated to the other hepatitis viruses, except that they all cause inflammation of the liver. It is an RNA virus, and is therefore highly variable in its expression (many mutations during replication similar to HIV). This is one reason why it is able to evade the immune system. During infection, HCV exists as many similar, but not identical, species (quasispecies) generally within the same genotype. There are nine genotypes (numbers 1–9), within which there are subtypes (letters a, b, c), so a viral infection is known as, for

example, 1a or 3a or 2b, etc.). Genotypes 1, 2, and 3 are widely distributed throughout the West and in East Asia (Japan, China, Taiwan, Thailand). Types 5 and 6 are mainly confined to South Africa and South-East Asia, respectively, in contrast to type 4, which is predominant in the Middle East and Central Africa.

HCV is transmitted primarily by blood-to-blood contact. Sharing injecting equipment and blood transfusion are the most efficient mechanisms of transmission. The rate of vertical transmission (mother to child) is low (<5%). The most important factor in vertical transmission is the level of virus in the mother (high level relates to a high chance of transmission). Sexual transmission is remote in mono-infection due to HCV. In HCV/HIV coinfection, sexual transmission is more common, though still very low. Hepatitis C viral load can be substantially higher in the presence of co-morbid HIV infection. Factors increasing the sexual transmission of hepatitis C in coinfection are high hepatitis C viral load, trauma during sex and possibly the presence of a sexually transmitted infection (STI).

NATURAL HISTORY

The natural history of HCV infection is relatively benign, at least in the first few years of infection. Once transmitted, a viraemia develops. This is followed by seroconversion (development of antibodies to hepatitis C), which takes between six weeks and six months to occur. Acute infection is asymptomatic in 60% of individuals. Common symptoms include fatigue, lethargy, nausea and other constitutional symptoms. Jaundice is uncommon and occurs in <25% of individuals.

Acute infection spontaneously clears in about 15% of individuals. This generally occurs within the first three to six months of treatment. There is no relationship between the genotype of HCV infection and the likelihood of clearance. The presence of HIV or other immunosuppression markedly reduces the likelihood of viral clearance. The rate of clearance among HIV-positive individuals is between 5% and 8%. If the virus is not cleared within the first few months of treatment, it is very unlikely that viral clearance will occur. Individuals with HIV coinfection generally have substantially higher viral loads than HCV mono-infected individuals.

Chronic HCV infection has an indolent course. Around one third of individuals with chronic hepatitis C infection have mild hepatitis with normal liver function tests (LFT). The other two third have abnormal LFT with moderate to severe inflammation. The rate of cirrhosis (significant liver scarring resulting in impaired liver function) is around 20% in those with chronic hepatitis after 20 years of infection.

Figure 3. Typical serological course of hepatitis C

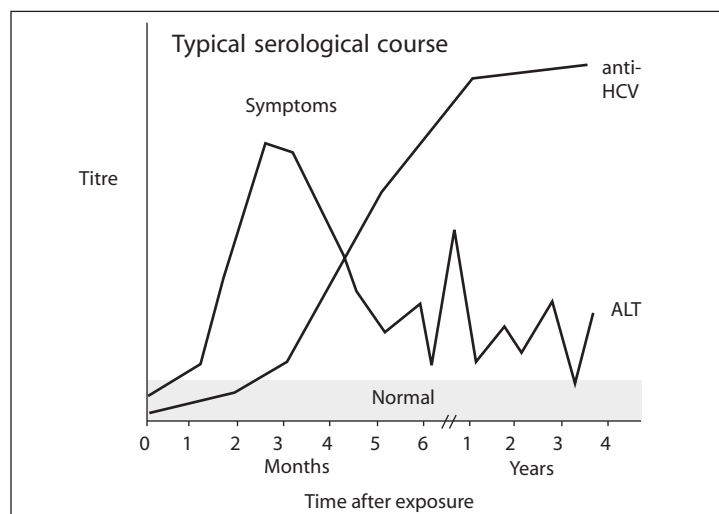
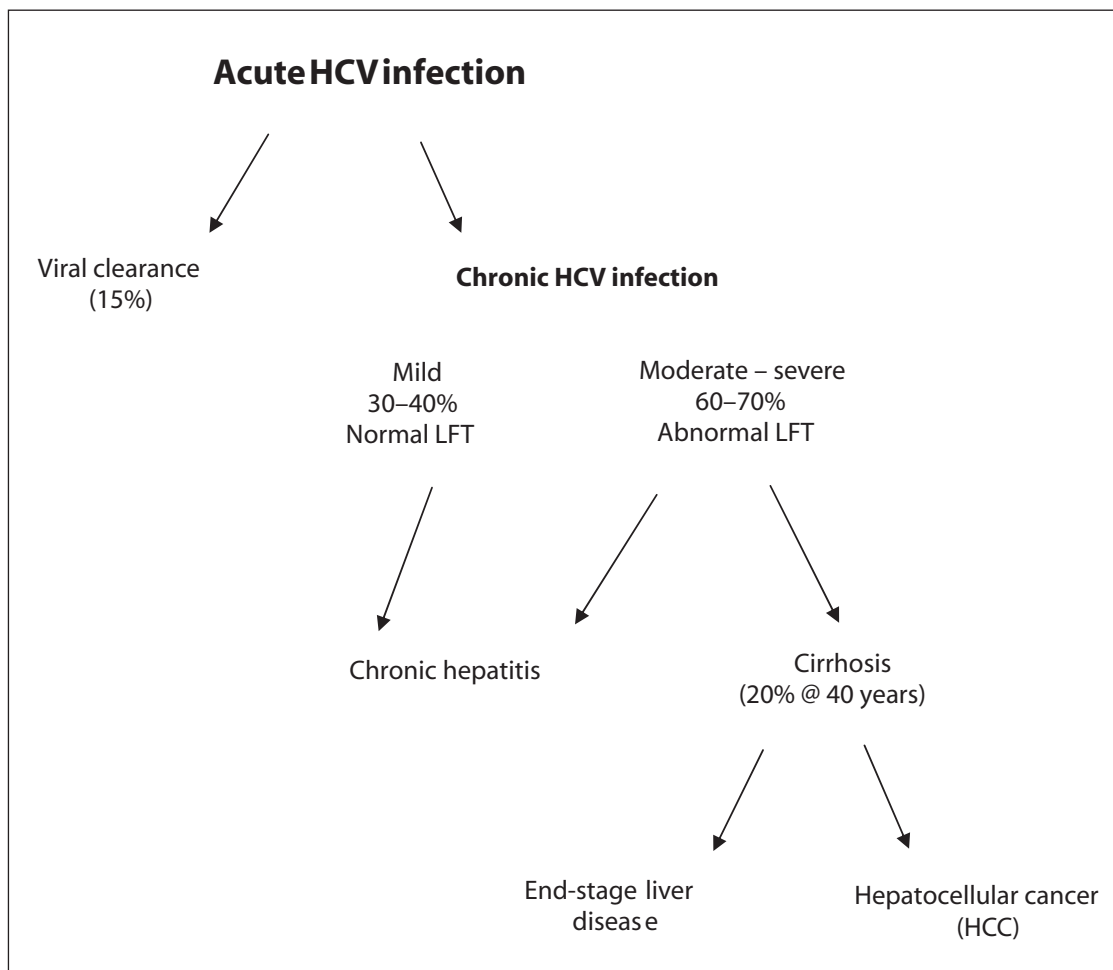


Figure 4. The course of HCV infection

EFFECT OF HCV ON HIV PROGRESSION

The effect of HCV on HIV progression is somewhat controversial. A number of studies have demonstrated that HCV may accelerate the course of HIV infection. The mechanism is not well known, although HCV is known to have immunomodulatory effects. A number of studies have also demonstrated that when controlled for influencing variables such as CD4 count, age and whether or not on antiretroviral therapy (ART), there is no difference in the progression of HIV between HCV/HIV coinfecting and HIV mono-infected individuals. The latter variable (ART) is probably the most important factor. Coinfection is much more common in IDUs, who often have reduced access to effective HIV treatment, thus differences in disease outcome may be attributable to differences in HIV treatment access.

EFFECT OF HIV ON HCV PROGRESSION

HIV does influence the progression of HCV in coinfection. Infection with HIV has been shown to result in a higher hepatitis C viral load, liver fibrosis, progression to cirrhosis, liver failure and hepatocellular carcinoma (HCC). Factors associated with an increased risk of liver disease progression in people with HIV/HCV coinfection include heavy alcohol (ethanol) intake (>50 g/day), older age at HCV acquisition, low CD4 count, increased quasispecies variability and occult hepatitis B virus (HBV) infection.

Despite this, adequate immune reconstitution with ART has been shown to modify the course of HCV in HIV infection including slowing the rate of progression of liver fibrosis and reducing complications from HCV. Better survival rates among individuals with HIV treated with effective ART have also increased the proportion of liver-related mortality and morbidity in developed countries.

Hepatitis C information: do and avoid

DO

- Vaccinate against hepatitis B and A if required
- Go for regular health check-ups
- Stop or reduce alcohol intake: alcohol use *significantly* increases the risk of developing cirrhosis and liver cancer
- Protect from *reinfection*: the presence of hepatitis C antibodies will *not protect* one from getting infected again
- Eat a balanced diet of fresh vegetables, fruits, beans, whole grains and lean meats; a healthy balance of protein in the diet
- Drink lots of fluids
- Exercise regularly
- Follow a stress reduction plan

AVOID

- Drinking alcohol; even one drink a day can accelerate the progression of liver disease
- Taking large amounts of acetaminophen (paracetamol) as it is toxic to the liver
- Taking acetaminophen and alcohol as together they can cause severe liver damage
- Breathing in pollutants, chemicals, cleaning products, fumes from paint, paint thinners, chemical solvents, spray adhesives, insect sprays and cleaners as these can be harmful to the liver
- Foods with high salt, sugar or fat content
- Too much fried foods
- High doses of vitamins A, D, E or K
- Taking iron supplements unless advised by the doctor

TREATMENT OF HCV IN HIV COINFECTION

Hepatitis C treatment is expensive and this limits access to treatment in Asia.

Treatment regimen

Standard treatment is a subcutaneous injection of pegylated interferon (PEG-IFN) weekly in combination with ribavirin (RBV) tablets or capsules (dose depending on weight and genotype) twice daily. The duration of treatment for HIV/HCV coinfection is 48 weeks for all genotypes. In HCV mono-infection, the treatment length can vary, depending on the genotype.

There are two companies that manufacture PEG-IFN, and the dosage will vary depending on the brand used. Pegasys (Roche) is PEG-IFN α 2a and is a standard dose for all weights; PegINTRON (Schering Plough) is PEG-IFN α 2b and the dose varies depending on the weight of the individual. Standard IFN was used in the past, but needs to be administered three times a week and is much less effective.

Effectiveness (sustained virological response)

It is necessary to understand the HCV treatment terminology of HCV infection.

Early virological response (EVR)	Usually a reduction in viral load 12 weeks into treatment, though this varies by level of reduction and timing
End-of-treatment response (ETR)	Undetectable HCV RNA at the end of treatment
Sustained virological response (SVR)	Undetectable HCV RNA at 24 weeks after completion of treatment. Obtaining a sustained virological response is often referred to as a "cure"
Non-responder (NR)	No significant reduction in HCV RNA levels (<2 log ₁₀) after a specified interval of treatment (usually 24 weeks), or no significant decrease in HCV RNA, but HCV RNA never becomes undetectable during treatment. Some non-responders may have improved liver histology after treatment
For further information go to www.fda.gov/ohrms/dockets/ac/06/slides/2006-4250s1-05-FDATAuber.ppt	

Combination PEG-IFN and RBV treatment is effective, with sustained virological response (SVR) rates of between 27% and 40% overall, and up to 73% in genotypes 2 and 3. The treatment of acute hepatitis C in the context of HIV coinfection may be more effective, with an SVR of just over 70% regardless of genotype.

A number of studies have shown that it is possible to treat active IDUs for HCV mono-infection and achieve good outcomes. However, few studies have looked at HCV treatment in HIV-coinfected active IDUs.

HCV treatment is more effective with better immune function and treatment is most effective with adequate immune function. It is recommended that ART be commenced in individuals with a CD4 count of less than 200 cells/mm³ prior to initiation of treatment for HCV. As a consequence, appropriate ART regimens and effective ART for IDUs in Asia will facilitate effective HCV treatment when this becomes more widely available.

If the CD4 count is <200 cells/mm³ then treat HIV first; once a CD4 count >350 cells/mm³ is reached treat HCV. If the CD4 count is >200 cells/mm³, then it is reasonable to treat hepatitis C first.

Reinfection and relapse

There are limited data on reinfection and relapse in HIV/HCV coinfection though it appears that reinfection rates are low. Necessary precautions are advised if injecting continues during and after completion of hepatitis C treatment (e.g. the use of clean needles and syringes, and sterile injection techniques).

Reinfection refers to infection with a new HCV. The reinfection rate in coinfection is unknown. In HCV mono-infection it is less than 5%. Relapse refers to a re-emergence of the same virus strain, usually relating to viral suppression during treatment beyond the detectable limit and increasing replication post-treatment, bringing the viral load back into the detectable range. The likelihood of relapse is reduced with combination treatment (PEG-IFN and RBV) compared with monotherapy

(PEG-IFN only). With combination treatment, the relapse rate is around 10% in genotype 1 and 2% in genotypes 2 and 3. This means that between treatment completion and six months after treatment completion, about 10% of genotype 1 HCV moves from being undetectable to becoming detectable, while only 2% of genotypes 2 and 3 do. Information on other genotypes is not available.

Feasibility

Interferon-based hepatitis C treatment regimens are difficult to tolerate. Side-effects are many and varied, and patients may need significant psychosocial and medical support. Depression is a very common side-effect and many IDUs may require antidepressant medication by the end of treatment. Selective serotonin reuptake inhibitors (SSRIs) are the first line of therapy in the management of depression during IFN treatment. There is currently no consensus on the use of prophylactic SSRI.

Combination PEG-IFN and RBV therapy:

Contraindications: Severe cardiac disease (<6 months prior); haemoglobinopathies (e.g. thalassaemia, sickle cell anaemia); creatinine clearance <50 ml/min; decompensated liver cirrhosis; recent, current immunosuppressive therapy (except short-term steroid); autoimmune disease; immunosuppressed transplant patients; uncontrolled thyroid disease; pregnancy, male partners of pregnant women (use contraception for longer than or for 6 months after treatment conclusion), lactation

Precautions: Cardiac, renal disease (monitor); ensure adequate hydration; severe hepatic dysfunction; initial, ongoing laboratory test monitoring (see full product information); diabetes, hypertension (monitor visual function); severe psychiatric conditions (including history); psoriasis; sarcoidosis; the elderly; children <18 years

Adverse reactions: Possibly teratogenic; bone marrow suppression; haemolysis; fever; ocular, pulmonary, cardiovascular effects; local reactions; fatigue; flu-like symptoms; infection; headache; rigors; gastrointestinal upset; anorexia; arthralgia, myalgia; psychiatric, CNS disturbance; insomnia; alopecia; pruritus; dry skin; dental, periodontal disorders; kidney, liver graft rejection (possible); hypertriglyceridaemia; thyroid dysfunction; autoantibody development; autoimmune disorders including thrombocytopenic purpura; gout; others, see full product information

Drug interactions: Nucleoside analogues including didanosine (ddl), stavudine (d4T), zidovudine (AZT); CYP1A2, CYP2C8/9, CYP2D6 metabolized drugs; *shosaikoto* (Chinese herb)

Particular attention should be paid to patients with cirrhosis. There is a higher risk of liver decompensation during anti-HCV treatment in those with cirrhosis. These individuals should be managed in collaboration with a gastroenterologist or hepatologist.

Alcohol use should be discouraged during treatment. This impairs the effectiveness of treatment, particularly when drinking is above 10 g ethanol equivalent per day (1 small beer).

Substance use should ideally be treated and stabilized prior to initiation of treatment, with continued management during treatment. Opiate dependence is ideally managed with opioid substitution therapy (OST). Clean injecting equipment should be accessible in case of relapse or continued heroin or other injecting drug use.

TREATMENT OF HIV IN HCV COINFECTION

It has become clear that effective HIV treatment (ART) reduces the progression of liver disease in HIV/HCV coinfecting individuals. Despite this, there are a number of precautions that need to be taken.

Hepatotoxicity

Abnormal liver function tests are common in HIV/HCV coinfecting individuals on ART. Severe dysfunction can lead to hepatotoxicity (markedly abnormal liver function, alanine aminotransferase [ALT] >5x upper limit of normal [ULN]). The mechanism is unclear but may be a combination of the direct effect of medication on the liver cells or a hypersensitivity reaction. Additionally, restoration of immune function with ART may induce immune reactions against the liver cells, causing liver damage – this is known as IRIS (see Sub-module 6.5).

NNRTI-based regimens

The WHO 2006 guidelines recommend that efavirenz (EFV) is the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) option wherever possible in patients who have HIV and hepatitis C coinfection. It is recommended that nevirapine (NVP) be used with care and regular monitoring done in patients who have known HIV/HCV coinfection and grade 3 or lower elevation of ALT. NVP is not recommended for those with ALT elevations of grade 4 or higher.

NTRIs

Nucleoside reverse transcriptase inhibitors (NTRIs) have been associated with hepatic steatosis leading to some hepatic dysfunction. Only limited data are available, and generally NTRIs are well tolerated during HIV treatment in coinfection.

PI-based regimens

Protease inhibitors (PIs) affect the liver either directly or by affecting the metabolism of other drugs to hepatotoxic ranges. Ritonavir (RTV), particularly at higher doses, has been associated with increased liver function abnormalities and hepatotoxicity. The risk of hepatotoxicity is more than doubled in HIV/HCV coinfection compared with HIV mono-infection.

Choice of ART regimen

The decision as to what ART regimen should be used in the treatment of HIV/HCV coinfection depends on the individual. NVP should possibly be avoided in moderate to severe liver dysfunction. Liver function should be monitored at treatment initiation and throughout treatment.

Monitoring during initiation and treatment

IDUs with HIV should be tested for HCV antibody prior to HIV treatment initiation. A positive test in the presence of abnormal liver function tests (particularly ALT) should indicate HCV infection. Individuals should be vaccinated against HBV if necessary and if the CD4 count >200 cells/mm³, and asked to avoid alcohol. The LFT should be monitored.

CONCLUSION

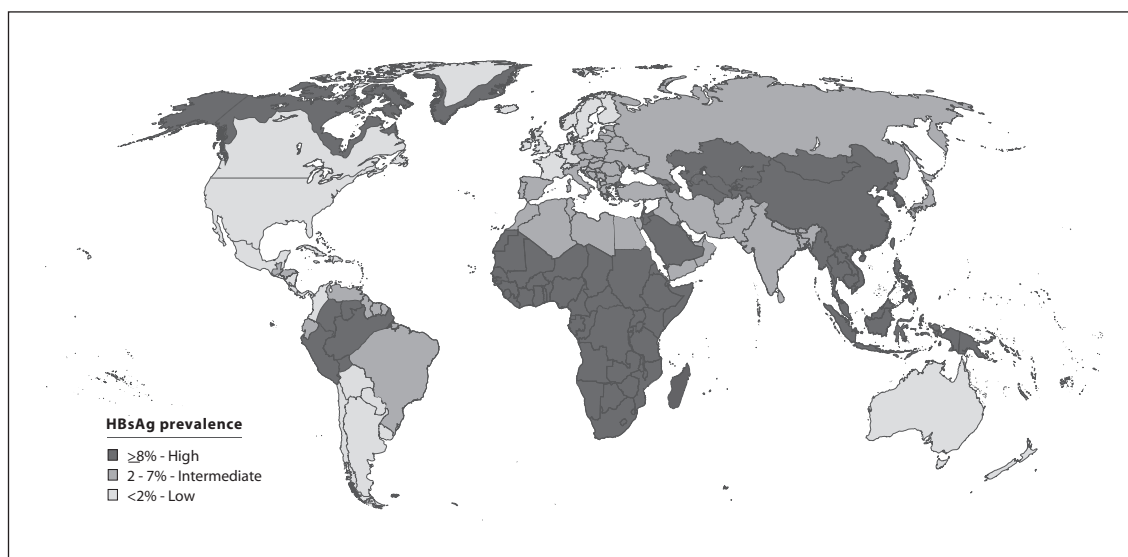
- HIV/HCV coinfection is very common in HIV-positive IDUs.
- Test for HCV-Ab + LFT prior to initiating ART.
- Treat HIV first if CD4 count <200 cells/mm³, then HCV if drugs are available.
- Avoid alcohol, treat substance use.
- Advise use of sterile injecting equipment.
- Use EFV instead of NVP for those with HIV/HCV coinfection.
- It is possible to use NVP in individuals with $<$ grade 3 elevation of ALT if LFT can be monitored regularly.
- Do not use NVP if there is grade 4 elevation of ALT.

HEPATITIS B COINFECTION

Epidemiology

There are over 400 million people living with chronic hepatitis B worldwide, although it is estimated that one third of the world's population has – at some stage – had HBV infection. The vast majority are in developing countries, including Asia where infection is endemic among neonates and infants. Indeed, hepatitis B is endemic in all of Africa, some parts of South America, Alaska, northern Canada and parts of Greenland, eastern Europe, the eastern Mediterranean area, South-East Asia, China and the Pacific Islands, except Australia, New Zealand and Japan. In most of these areas, 5–15% of the population are chronically infected carriers of HBV. HBV is also more common in IDUs in both developing and developed countries. In western Europe, North America and Australia the prevalence of HBV infection is less than 0.5%.

Figure 5. Geographical distribution of chronic HBV infection



Source: Epidemiology and prevention of viral hepatitis A to E: hepatitis B virus. Division of viral hepatitis, CDC slide set found at: <http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/index.htm>

Hepatitis B is transmitted vertically (mother to child) in about 5% of pregnancies among hepatitis B

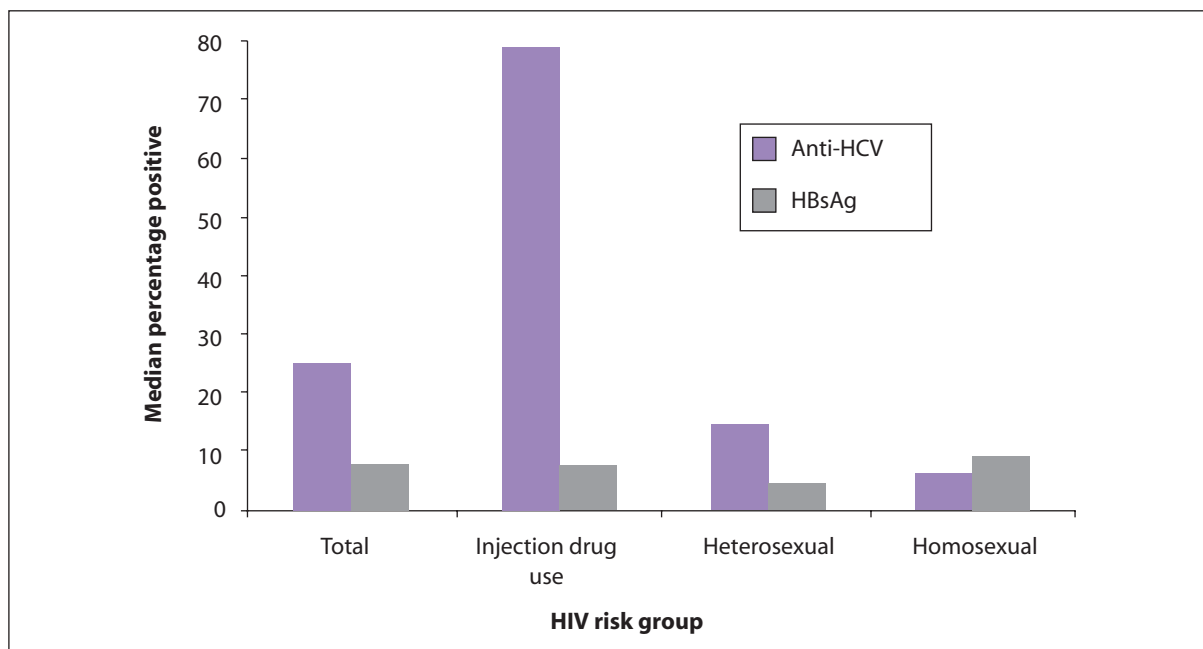
carriers, and horizontally through unprotected sex, sharing of injecting equipment and importantly through close contact particularly between infants and neonates (perinatal transmission). It is also transmitted through unsterile medical injections and unscreened blood products.

It is important to know how HBV is not transmitted. HBV is NOT transmitted through food or water, casual contact, such as hugging or shaking hands, or through kissing, sneezing or coughing. It is not transmitted through breastfeeding. Vaccination does not help individuals who are already infected with HBV.

Chronic infection with HBV occurs in 90% of individuals infected in the first six months of life, while if acute infection occurs in adults, >95% clear the virus completely.

The global epidemiology of HBV/HIV coinfection is less well understood. Due to the common pathways of transmission and endemic HBV infection in Asia, the prevalence of past exposure in IDUs is extremely high.

Figure 6. Prevalence of chronic HBV virus and HCV infection in HIV-positive populations by HIV risk group



Source: Nakata S et al. *Journal of Gastroenterology and Hepatology*, 1994

The virus and testing

Hepatitis B is a DNA virus of the Hepadnavirus family. It infects and replicates within the hepatocytes (liver cells) though it causes little or no damage to the cells. Liver damage is caused by the immune response to the virus and hence chronic infection results in greater hepatic dysfunction from a chronic immune response.

There are seven hepatitis B genotypes. A is pandemic, B and C are found in Asia, D in southern Europe, E in Africa, F in the USA, and G in the USA and France. There appears to be little difference in the extent of disease caused by the different genotypes, although genotype C has been associated with more severe and prolonged disease and may be more difficult to treat. There are a number of different components of the virus that have been identified, which are useful in assessing an individual's state of infection.

Table 1. Markers of hepatitis B disease

Marker	Full form	Indicates
HBsAg	Hepatitis B surface antigen	Current infection with hepatitis B (a carrier)
HBsAb	Hepatitis B surface antibody	Immunoprotection against hepatitis from either vaccination or previous exposure
HBcAb	Hepatitis B core antibody	Previous exposure to hepatitis B
HBeAg	Hepatitis B e antigen	Marker of active replication/active disease
HBeAb	Hepatitis B e antibody	Marker of inactive disease, so called "e seroconversion"
HBV DNA	Hepatitis B DNA	Presence indicates active replication and disease. Amount of DNA is "HBV viral load"

Source: WHO, 2002.

Table 2. Interpretation of hepatitis B tests

Test combination	Results	Interpretation
HBsAg HBcAb HBsAb	- - -	Susceptible to hepatitis B
HBsAg HBcAb HBsAb	- + +	Past history of HBV with current immunoprotection
HBsAg HBcAb HBsAb	- - +	Immune due to hepatitis B vaccination
HBsAg HBcAb HBsAb	- + -	Past history of HBV infection

Source: WHO, 2002.

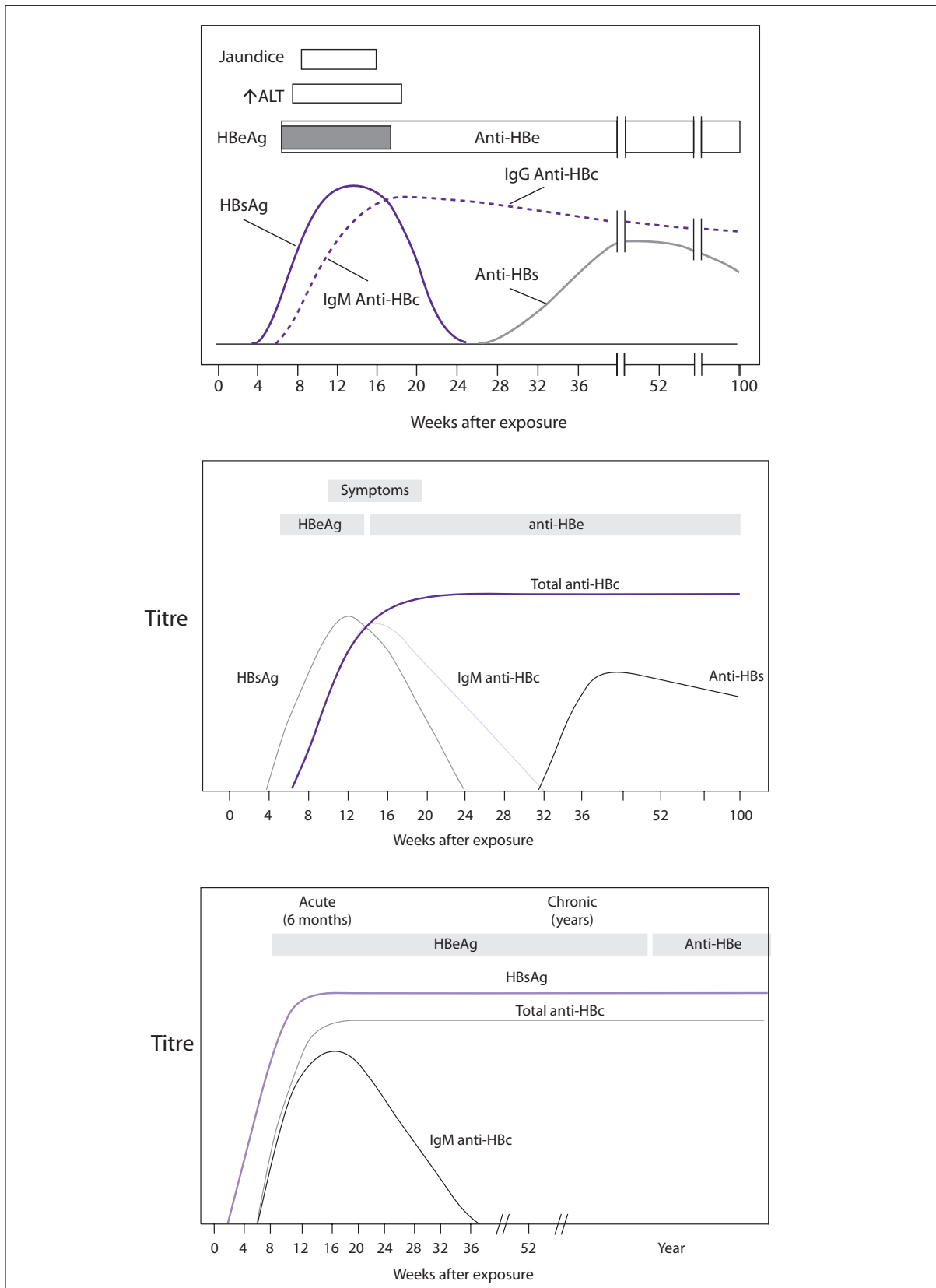
All IDUs should be tested for hepatitis B, especially if treatment for HIV is to begin. Testing in HIV-positive individuals is more difficult, as markers of the disease may not always be present. Initial tests should include HBsAg and if possible HBsAb and HBcAb. In HIV-positive individuals, HBsAg may be negative although the virus is present and therefore, if available, HBV DNA should be done for confirmation of the disease (occult HBV infection).

NATURAL HISTORY

In infancy and early childhood (<2 years old) acute infection is usually asymptomatic but much more likely to result in chronic infection (>90% of individuals <6 months). In adulthood, acute infection is usually symptomatic with jaundice, nausea, fatigue and lethargy in 75% of people, but only <5% go on to have chronic infection. The presence of HIV is more likely to result in chronic infection.

In the presence of HIV, HBV viral replication and therefore its viral load are higher. Liver injury is usually reduced with immunosuppression such as in HIV infection. In some people with very high viral loads, HBV can directly cause injury to the liver cells (known as fibrosing cholestatic hepatitis).

Figure 7. Natural history of hepatitis B



Source: World Health Organization. *Hepatitis B*. Geneva, WHO, Department of Communicable Diseases Surveillance and Response, 2002. http://www.who.int/csr/disease/hepatitis/HepatitisB_who.cdscsr.lyo2002_2.pdf

EFFECT OF HBV ON HIV PROGRESSION

Early studies in the pre-ART era suggested that HBV infection could be a cofactor in HIV disease; however, more recently it has become clear that this is not the case when other factors are taken into consideration. Evidence from the ART era has suggested that HBV does not appear to alter the course of HIV.

EFFECT OF HIV ON HBV PROGRESSION

HIV coinfection influences the course and natural history of HBV infection by impairing the quantity and quality of the innate and adaptive immune response. The rates of spontaneous resolution after acute infection and spontaneous anti-HBe and anti-HBs seroconversion are decreased, and levels of HBV replication are increased in HIV-infected patients. A more rapid progression of liver fibrosis and a higher rate of cirrhosis leading to decompensation (but not HCC) have been demonstrated in coinfecting patients. The risk of HBV-associated end-stage liver disease (ESLD) and liver-related mortality may be increased by HIV coinfection.

ART can have a major impact on HBV coinfection because of the restoration of immune responses and improved regulation of the immune system. In addition, at least three ARVs (3TC, TDF and FTC) are potent inhibitors of HBV replication. There is also some evidence that 3TC may prevent acute hepatitis B infection in HIV-positive individuals exposed to hepatitis on an ART regimen that contains 3TC.

TREATMENT OF HBV IN HIV COINFECTION

Prevention

There is an effective vaccine available for the prevention of hepatitis B. All at-risk individuals who are not immunoprotected (no HBsAb nor HBcAb) should be vaccinated. Those who are HIV-positive are less likely to respond to HBV vaccine (especially if the CD4 count is <200 cells/mm³), have lower mean antibody titres (by a factor of about 30), and lose protective antibody levels more quickly.

The vaccination regimen in coinfection should be 0, 1, 6 months or 0, 1, 2, 12 months. Non-responders should have a further three shots at double the dose.

Treatment regimen

Treatment of hepatitis B in HIV coinfection is complex. HIV coinfecting individuals are less likely to respond to treatment, yet a number of agents used to treat hepatitis B are also used to treat HIV.

There are a number of drugs registered to treat hepatitis B: 3TC (a nucleoside analogue), adefovir, dipivoxil (nucleotide analogue reverse transcriptase inhibitor), entecavir (a purine-derived nucleoside analogue) and PEG-IFN $\alpha 2a$; TDF (a nucleotide reverse transcriptase inhibitor) and FTC are also effective in suppressing HBV.

3TC inhibits HBV replication in up to 87% of HIV/HBV coinfecting patients, while anti-HBe seroconversion occurs in up to 11% of patients. Mutations in the replication mechanism of HBV lead to resistance to 3TC in 47% of patients at two years and 90% at four years of treatment.

Adefovir dipivoxil taken 10 mg PO daily has been shown to reduce the viral load though resistance does develop. In combination with 3TC, resistance is less likely.

TDF has been shown to be effective in treating hepatitis B in coinfecting individuals and there is no evidence of resistance developing. It is also effective against 3TC resistant hepatitis B.

Entecavir has been shown to reduce the hepatitis B viral load in coinfecting individuals with a low risk of development of resistance by HBV and by HIV to ART. Its suggested use is in people not requiring ART.

PEG-IFN (48 weeks of weekly 180 log subcutaneous injection) has been shown to be more effective than 3TC in inducing HBeAg seroconversion, reducing the viral load and in normalizing liver function.

Side-effects: 3TC is well tolerated and safe; however, development of HBV resistance is frequent. Adefovir has a nephrotoxic potential and may at least theoretically induce ARV resistance in HBV/HIV patients treated with it. TDF has gastrointestinal side-effects, is associated with hypophosphataemia that has not been known to induce serious osteopenia so far, and may have a nephrotoxic potential.

The following treatment is recommended (Australasian Society for HIV Medicine 2003):

In individuals requiring HBV treatment but not HIV treatment:

It is reasonable to delay treatment for hepatitis B. If treatment is desired then use PEG-IFN or a non-ART agent to avoid the development of resistance to the agent (e.g. entecavir or adefovir dipivoxil).

In individuals requiring both HBV treatment and HIV treatment:

ARVs with HBV activity should be included in the regimen. If a single agent is used, TDF has a better resistance profile. If two agents can be used then 3TC and TDF should be used. 3TC can be used alone but HBV resistance will eventually occur.

In individuals not requiring HBV treatment, but requiring HIV treatment:

If hepatitis B replication is under control (HBV DNA $<4 \log^{10}$ copies/ml), ART need not contain agents with dual activity. The type of ART regimen should be determined as per usual indications.

In individuals with resistance to 3TC:

Suspect if the HBV viral load increases by $1 \log^{10}$ copies/ml. Add TDF to the regimen if only 3TC is being used. Switching to adefovir or entecavir can also be done.

In individuals with cirrhosis:

These patients are at risk for hepatic decompensation (failure) when ART is initiated, particularly if the CD4 count is low and viral load of HBV is high. Therefore, use a combination (e.g. 3TC + TDF) initially to reduce the viral load before commencing full ART.

Treatment of HBV is expensive, and therefore inaccessible to many people. In resource-poor settings, the key issues are:

- Vaccination for hepatitis B
- Stabilization of drug use with appropriate treatment (e.g. OST)
- Reduction and ideally cessation of alcohol use
- Use of ARVs in the treatment of HIV with activity against HBV.

Effectiveness

Limited data are available on the effectiveness of HBV treatment in HBV/HIV coinfection.

Effectiveness of HBV treatment can be measured by:

- HBV DNA level:
 - ◆ This is called the HBV viral load and is the best way to monitor the effectiveness of treatment. It is also the most expensive.
 - ◆ 3TC reduces the viral load by almost 3 log¹⁰ copies/ml after 1 year of treatment.
 - ◆ Adefovir dipiroxil reduces viral load by 4 log¹⁰ copies/ml after 1 year of treatment.
 - ◆ TDF reduces the viral load by 4 log¹⁰ copies/ml regardless of resistance to 3TC.
- HBeAg seroconversion:
 - ◆ This signifies the development of HBeAb as a result of treatment and indicates control of replication.
 - ◆ Only a minority of individuals on treatment will have HBeAg seroconversion.
- ALT levels:
 - ◆ ALT levels are an inexpensive way to monitor therapy, but can be difficult to interpret.
 - ◆ There is a clear correlation between the decrease in viral load and reduction in ALT levels.
 - ◆ There is also a clear correlation between improvement in ALT levels and that of liver histology scores during therapy.
 - ◆ ALT can rise during:
 - Control of viral replication (due to restoration of immune function)
 - Liver toxicity from drug therapy.

Resistance

Resistance is more common with 3TC therapy and less so with adefovir dipiroxil or TDF. Mutations that explain resistance have been identified, but resistance testing is expensive and often unavailable.

It is important to remember that TDF is active against 3TC-resistant HBV.

TREATMENT OF HIV IN HBV COINFECTION

This is discussed above, but the important aspects are:

- It is usually unnecessary to treat HBV infection when there is no indication for HIV treatment. Additionally exposing the individual to the development of resistance to ARVs is unwise.
- When HIV treatment is indicated, use a regimen with agents such as 3TC and/or TDF, which also have activity against HBV.
- In individuals with cirrhosis, low CD4 counts and high HBV viral load, control HBV replication prior to starting ART.
- EFV is the preferred NNRTI option in individuals with HBV/HIV coinfection.
- NVP may be used with care and regular monitoring in patients who have known HBV/HIV coinfection and ≤grade 3 elevation of ALT.
- NVP is not recommended for those with ≥grade 4 ALT elevation.

HBV flares on ART

HBV flares may occur during ART in HBV/HIV coinfection as a presentation of the immune reconstitution inflammatory syndrome (IRIS). Flares are characterized by an acute rise in hepatic transaminases accompanied by symptoms of acute hepatitis (fatigue, abdominal pain and jaundice). These reactions generally occur during the first few months of treatment and may be difficult to distinguish from ART-induced hepatic toxicity. Drugs active against HBV should preferably be continued during a suspected flare, and, if the patient is receiving 3TC monotherapy, consideration should be given to the addition of TDF if available. If it is not possible to distinguish a serious hepatitis B flare from a grade 4 ART toxicity, all ARV drugs should be withheld until the clinical condition improves.

HBV flares when ART is stopped

There is also a risk of a flare of HBV when HBV-active drugs are stopped. Fatal cases of acute HBV infection have been documented in HBV/HIV coinfecting patients who discontinue 3TC monotherapy. Patients with coinfection who need to stop the HBV-active drugs in the HIV treatment regimen (3TC, FTC or TDF) should be closely monitored. If a patient is known to have chronic HBV, it is recommended that 3TC be continued as part of second-line ART following initial ART failure, even if it has been used in first-line treatment.

CONCLUSION

- Hepatitis B is very common in HIV-positive IDUs.
- All HIV-positive IDUs should be screened for HBV.
- All HIV-positive IDUs should be vaccinated against HBV if not already immunoprotected.
- Treatment for hepatitis B should generally be withheld until there is an indication to treat HIV.
- HIV treatment regimens in the context of hepatitis B should incorporate agents that have activity against hepatitis B.
- ALT should be monitored during HBV treatment.
- TDF should be used in case of 3TC resistance.
- EFV is the preferred NNRTI option in individuals with HBV/HIV coinfection.
- NVP may be used with care and regular monitoring in patients who have known HBV/HIV coinfection and \leq grade 3 elevation of ALT.
- NVP is not recommended for those with \geq grade 4 ALT elevation.

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Management of HIV/TB coinfection in IDUs

OVERVIEW



Objectives:

By the end of the session participants will be able:

- To describe the epidemiology of TB among IDUs and PLWHA
- To use the WHO guidelines to prescribe co-trimoxazole prophylaxis in HIV-infected patients
- To describe care and treatment interventions for HIV-infected IDUs with active TB
- To appropriately use ART in HIV-infected IDUs with active TB



Time to complete session:

1 hour 15 minutes



Session content:

- Care and support for HIV-infected individuals with active TB
- Co-trimoxazole preventive treatment and HIV-associated active TB
- Principles of antiretroviral therapy



Training materials:

- PowerPoint presentation 9.2: Management of HIV/TB coinfection in IDUs
- Sub-module 9.2: Management of HIV/TB coinfection in IDUs
- Exercise 9.2.1: Case studies 1, 2, 3

CARE AND SUPPORT FOR HIV-INFECTED INDIVIDUALS WITH ACTIVE TB

Background

The public health approach to decrease the burden of TB/HIV requires more effective delivery of the available interventions for HIV-infected individuals including those with TB/HIV coinfection or active TB disease by health service providers. Increased population coverage by these interventions is also needed. HIV-infected patients, including those with active TB, should benefit from HIV/AIDS care, treatment and support.

Whereas previous national TB and AIDS programmes have largely pursued separate courses, they need to look for synergy in supporting health service providers to deliver care and treatment for HIV-infected individuals with TB. A key operational issue is that HIV programmes are largely vertical, with care centred in a small number of tertiary referral centres or specialized clinics in most countries. TB programmes are administratively vertical, but services are disseminated and integrated into the primary health-care systems down to the sub-district/health centre level. Other issues remain in determining optimal cross-referral procedures, care integration and patient monitoring. Significant administrative, social, stigma-related and ethical barriers to successful collaboration remain to be addressed. Thailand is the only country in the Region, and one of the few in the world, where TB and HIV services are equally decentralized down to the sub-district level.

Concept of comprehensive HIV/AIDS care

Comprehensive HIV/AIDS care is a holistic approach to meeting the needs of HIV-infected individuals. Several studies have been conducted in the Asia-Pacific Region to assess the needs of persons living with HIV (PLWHA). The following needs were identified (WHO SEARO, 2002a).

Providing comprehensive HIV care includes:

- Clinical and nursing care for those affected to alleviate the symptoms of HIV disease
- Psychosocial support and ongoing counselling
- Financial support or employment opportunities for PLWHA
- Housing and legal assistance
- Care and support for orphans and widows
- Information and training of caregivers and affected people.

Comprehensive care should link the formal (health facilities including health centres) and informal (family and community care) sections of the health system in a cohesive network of services. The success of a *comprehensive continuum of care model* depends on the cooperation and collaboration of health-care workers at all levels (primary, secondary and tertiary) and the active involvement of communities at risk, PLWHA and their families and caregivers. The “continuum of care” stands for the seamless movement of PLWHA to and from the formal to the informal health services.

If comprehensive care across the continuum operates successfully, then it will facilitate:

- An improvement in the duration and quality of life of PLWHA
- A reduction in the level of stigma and discrimination in clinical and community care settings
- Alleviation of the impact of HIV and AIDS

The comprehensive care model builds on the existing health system. Strategies to provide comprehensive care include:

- Involving formal and informal health-care services at the district and sub-district levels in the national scale-up plan
- Defining the roles of each institution and health cadre at all levels of care including monitoring and supervision
- Defining and/or establishing referral networks so that PLWHA can access appropriate services when they are needed
- Establishing formal linkages between community-based and facility-based services to regularly exchange information and strengthen partnerships between care providers
- Capacity building including at the district and sub-district levels and developing appropriate training tools and methodologies
- Providing appropriate opportunities for health-care workers and care providers (both formal and informal) to identify gaps in skills and services.

The full involvement of PLWHA peers in HIV services such as in day-care centres or centres for comprehensive and continuous care is a key approach for ensuring treatment adherence and facilitating follow up of people.

Experience from Thailand

The consortium of Thai Network for People Living with HIV/AIDS (TNP-plus) and other NGOs received support from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) in 2003 to strengthen PLWHA involvement in the comprehensive continuum of care (CCC) centres. As of October 2004 the programme had been expanded to 114 hospitals and one women's prison covering nearly 10 000 PLWHA on care and treatment. The number of PLWHA followed in each CCC centre ranged from 6 to 350. PLWHA support groups provide education on ART literacy and peer counselling including for treatment adherence. They also work as volunteers for providing logistic support to health-care workers and patients such as filling in forms, transporting files, problem-solving, conducting inpatient visits, providing outreach for home care and support, and tracing of defaulters. PLWHA disclose their HIV status upon entering the PLWHA group. At the district level this implies disclosure of the HIV status to the family and community. These groups allow PLWHA to address factors that may affect their adherence to ART, such as side-effects, lack of family and emotional support, lack of treatment information and advice on taking pills regularly and on time. PLWHA groups and NGOs also support and encourage enrolment in the national ART programme (Kumphitak et al. 2004).

Models for the delivery of HIV/AIDS care and treatment for HIV-infected TB patients, in particular during TB treatment, are less well described. Collaboration between the TB and HIV programmes is essential for the delivery of an integrated package of HIV and TB services for HIV-infected TB patients (WHO, 2004).

CO-TRIMOXAZOLE PREVENTIVE TREATMENT AND HIV-ASSOCIATED ACTIVE TB

Co-trimoxazole (CTX) preventive treatment is the gold standard in developed countries for HIV-infected individuals with CD4+ T-cell counts <200 cells/mm³ to prevent *Pneumocystis jiroveci* pneumonia (PCP), a common opportunistic infection (OI) with a high mortality (USPHA/IDSA, 2001). This common OI and other bacterial infections cause considerable morbidity during the treatment of HIV-infected TB cases. Studies have shown that preventive treatment with CTX against

these infections decreased morbidity and mortality in HIV-infected patients with TB disease in Africa. A study conducted in Côte d'Ivoire (Africa) showed a significant benefit of CTX prophylaxis against some bacterial causes of pneumonia and diarrhoea and their complications (Wiktor, 1999; Wagner, 2001; Havlir, 1999). A cohort study conducted in Malawi compared an HIV-seropositive TB cohort receiving CTX for 12 months with a historical comparison group who were not receiving CTX. Both cohorts received TB treatment as per the national directly observed treatment, short-course (DOTS) strategy. Survival of HIV-positive TB patients improved dramatically with the addition of CTX prophylaxis to the treatment regimen (Mwaungulu, 2004).

Data on the prevalence of OIs and the use of CTX are less well documented in Asian countries. PCP is the second most commonly reported OI in Thailand and India after TB (MOPH Thailand, 2003; Hira, 1998). The Thai *HIV/AIDS clinical management guidelines* recommend the use of CTX (MOPH, 2000). All HIV-infected patients with a CD4+ T-cell count <200 cells/mm³ are offered CTX in Thai health facilities. Further studies are necessary to evaluate the best models for the use of CTX in HIV-infected TB patients in Asia and the Pacific.

While all HIV-exposed infants and children should benefit from CTX preventive therapy, this intervention is particularly important in children coinfecting with TB and HIV.

WHO recommends the use of CTX preventive treatment in HIV-infected individuals as part of a minimum package of care for PLWHA (World Health Organization. *Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults: recommendations for a public health approach*. Geneva, Switzerland, WHO, 2006.).

PRINCIPLES OF ANTIRETROVIRAL THERAPY (ART)

Antiretroviral treatment and TB

Due to the high prevalence of TB among HIV-infected individuals living in the Asia-Pacific Region, many patients who are candidates for ART will have active TB (Narain, 2002). HIV-infected persons with active TB will often be offered ART because those with pulmonary TB meet the criteria for WHO stage 3 disease and those with extrapulmonary TB for WHO stage 4. ART may be highly beneficial in reducing case-fatality rates in these persons (Girardi, 2001; Badri, 2002). In addition, patients already receiving ART may develop clinical TB.

ART in individuals undergoing treatment for TB merits special consideration because co-management of HIV and TB is complicated by:

- Drug interactions between rifampicin and several classes of ARVs
- High pill burden
- Difficulties in adherence to treatment
- Drug toxicity
- Immune reconstitution inflammatory syndrome (IRIS) (Kwara, 2005)

The treatment of TB remains a central priority for patient care. TB treatment following the DOTS strategy should be initiated promptly in diagnosed cases of TB regardless of the HIV serostatus (Santoro-Lopes, 2002).

Other guidelines and materials should be consulted for more guidance on ART. In this rapidly evolving field, it is highly recommended to consult regularly updated treatment guidelines and the literature. The WHO websites are useful sources of up-to-date guidance (<http://www.who.int/HIV>, <http://www.searo.who.int/aids>, <http://www.wpro.who.int>). They also provide links to treatment-related websites.

Antiretroviral drugs in adults and adolescents

When to start ART in adults and adolescents

WHO recommends that in resource-limited settings, HIV-infected adolescents and adults should start ART when they have confirmed HIV infection and one of the conditions shown in Tables 3 and 4.

When to start ART in adults and adolescents with active TB disease

In HIV-infected persons being treated for TB, the optimal timing of initiation of ART is not known. On the one hand, case-fatality rates in patients with TB during the first two months of TB treatment are high, particularly in high HIV-prevalence settings, arguing for early treatment initiation (Corbett, 2003). On the other hand, considerations of drug interactions between rifampicin and several classes of ARVs, a high pill burden, toxicity and IRIS support the later initiation of ART.

Table 3. Recommendations for starting antiretroviral therapy in adults and adolescents with documented HIV infection if CD4 testing is available

Clinically advanced and severe/very advanced HIV disease	
WHO stage 4	Disease irrespective of CD4+ T-cell count
WHO stage 3	Consider using CD4+ T-cell counts <350 cells/mm ³ to assist decision-making ^a
Mildly symptomatic and asymptomatic disease	
WHO stage 2, 1	Treatment should be considered if CD4 cell counts ≤200 cells/mm ^{3b} Treatment should be considered in individuals with CD4 cell counts <350 cells/mm ³ , particularly if in the 200–250 cells/mm ³ range
<p>a CD4 cell count advisable to assist with determining need for immediate therapy. For example, pulmonary TB may occur at any CD4 level and other conditions may be mimicked by non-HIV aetiologies (e.g. chronic diarrhoea, prolonged fever).</p> <p>b The precise CD4 count above 200 cells/mm³ at which ART should be started has not been established.</p>	

Table 4. Recommendations for starting antiretroviral therapy in adults and adolescents with documented HIV infection if CD4 testing is not available

Clinically advanced and severe/very advanced HIV disease	
WHO stage 4	Irrespective of total lymphocyte count (TLC)
WHO stage 3	Irrespective of (TLC)
Mildly symptomatic and asymptomatic disease	
WHO stage 2	With TLC <1200 cells/mm ^{3a}
<p>a A TLC of ≤1200 cells/mm³ can be substituted for the CD4+ T-cell count when the latter is unavailable and there is moderate HIV disease (stage 2). It is not useful in asymptomatic patients. Thus, in the absence of CD4 testing, asymptomatic HIV-infected patients (WHO stage 1) should not be treated because there is currently no other reliable marker available in severely resource-constrained settings.</p>	

The optimum time at which to commence ART in a patient with TB/HIV coinfection is unknown. Initiation of ART is recommended for TB patients at very high risk for HIV disease progression and mortality. For patients with a CD4+ T-cell count <200 cells/mm³, ART is recommended as soon as the TB therapy is tolerated, usually between 2 weeks and 2 months (Table 5). For patients who develop TB with CD4+ T-cell counts in the 200–350 cells/mm³ range, ART should be started after the first two months of TB therapy, because the toxicity of TB treatment is greatest in the first two months of treatment. In patients with CD4+ T-cell counts >350 cells/mm³, ART should be deferred and the patient monitored closely.

Where CD4 counts are not available, WHO recommends that ART be considered after the intensive phase of TB treatment. Clinical judgement may indicate earlier or later initiation.

Table 5. ART recommendations for individuals with HIV-related TB if CD4 count is available

CD4+ T-cell count	Recommended regimen	Comments
<200 cells/mm ³	Start TB treatment. Start one of the regimens below as soon as TB treatment is tolerated (between 2 weeks and 2 months) ^a . EFV-containing regimen ^b	Recommend ART
200–350 cells/mm ³	Start TB treatment. Start one of the regimens below after initiation phase (if severely compromised start earlier).	Recommend ART
>350 cells/mm ³	Start TB treatment.	Defer ART ^c
Not available	Start TB treatment. Start one of the regimens below after initiation phase (if severely compromised start earlier).	Consider ART ^{a,d}

a Timing of ART initiation should be up to clinical judgement based on other signs of immunodeficiency.

b First-line treatment regimen alternatives to EFV- or ABC (300 mg bid)-containing regimens. For other alternatives please see text below.

c Unless non-TB WHO stage 4 conditions are present. Otherwise, consider ART upon completion of TB treatment.

d If no other signs of immunodeficiency are present and patient is improving on TB treatment, ART should be started upon completion of TB treatment.

First-line ART regimens in the setting of TB treatment for adults and adolescents

An NNRTI plus two NRTIs is the recommended first-line ART regimen in resource-limited settings. Accumulating data from these settings support the use of first-line NNRTI-containing ARV regimens in patients receiving rifampicin for TB.

EFV is the recommended NNRTI, but its use may be impaired by its limited availability in several nationally supported ART programmes and restrictions in pregnant women or women of childbearing age (Bristol-Myers Squibb Company, 2005). NVP is an alternative agent, but has a greater risk of hepatotoxicity, which can be life-threatening. This makes the drug less suitable for treating patients who use other hepatotoxic medications, such as rifampicin and for persons with high CD4+ T-cell count or for whom the CD4+ T-cell count is not known. Triple NRTIs (ABC + zidovudine [AZT] + 3TC or TDF + AZT + 3TC) are an additional option and can be used during pregnancy, in HIV-2 infection or in patients with higher CD4+ T-cell counts; data are limited to support this recommendation (Department of Health & Human Services, 2006).

Efavirenz + 2 NRTIs

EFV remains the NNRTI of choice. EFV blood levels are decreased in the presence of rifampicin. Until more data justify an EFV dose increase, WHO recommends the standard 600 mg dose of EFV, which can be administered as a once-daily tablet. Due to concerns related to teratogenicity, EFV should not be used in women of childbearing age (without adequate contraception) or those who are in the first trimester of pregnancy.

Nevirapine + 2 NRTIs

NVP should only be used if EFV is not available. For all patients receiving NVP plus rifampicin, close clinical and laboratory monitoring of liver enzymes is advised due to the increased risk of hepatotoxicity. NVP levels are also decreased in the presence of rifampicin. However, given the high therapeutic index of NVP, and the recent studies from South Africa and Thailand showing good short-term outcome related to antiviral activity and few adverse events in patients receiving both drugs, expert opinion states that dose adjustment may not be required (Autar, 2004; Oliva, 2003; Ribera, 2001; Dean, 1999; Van Cutsem, 2005). This area requires further investigation, as there is a large interpatient variability in NVP levels and exposure among HIV-infected persons, independently of any rifampicin interaction (Cozzi-Lepri, 2002). NVP is not recommended for women with CD4+ T-cell counts >250 cells/mm³ and men with CD4+ T-cell counts >400 cells/mm³ due to an increased risk of hepatotoxicity.

Triple NRTI

Triple NRTI therapy (ABC + AZT + 3TC or TDF + AZT + 3TC) is an alternative regimen for women likely to be or to become pregnant, in persons with higher CD4+ T-cell counts where the risk of NVP toxicity is increased and in special conditions such as HBV and HCV-induced hepatitis. Pregnant women can safely take ABC, 3TC and AZT. This regimen has no drug interactions with rifampicin. Concerns regarding this triple NRTI regimen are antiviral potency, limited data among patients with TB and monitoring for the hypersensitivity syndrome reaction (associated with ABC). TDF, 3TC and AZT have no or minimal interactions with rifampicin, but efficacy data are limited for patients with TB (Gulik, 2004).

Development of active TB in adults and adolescents receiving ART

ART decreases the incidence of TB in treated cohorts by approximately 80%, but rates of TB among treated patients nevertheless remain persistently higher than among HIV-negative individuals (Williams, 2003). Although recent evidence shows that TB should be considered as an advanced/late HIV OI, the development of an episode of TB still occurs across a wide range of CD4+ T-cell counts (Scano, 2005). In addition, subclinical or undiagnosed TB often presents within the first six months after initiation of ART (Seyler, 2005). For these reasons, it is difficult to determine if an episode of TB in a patient receiving ART indicates treatment failure and requires switching of the ART regimen.

Until further data are available, WHO recommends that if an episode of TB occurs in a patient receiving ART, an ART regimen compatible with the TB treatment regimen should be continued during TB treatment. If a person is receiving a NVP-based regimen, EFV should be substituted for NVP and continued until two weeks after rifampicin is completed, then EFV should be substituted for NVP. If EFV is contraindicated or not available, the NVP-based regimen should be continued during TB treatment with careful monitoring of liver function and drug toxicity.

ART second-line treatment options are limited for patients with TB with clear evidence of a failing ART regimen. The second-line treatment options are described elsewhere.

Immune reconstitution inflammatory syndrome

IRIS, a worsening of clinical disease after initial improvement, may occur in up to a third of persons with TB who initiate ART (see Sub-module 6.5).

The average time of onset is two months after ART initiation, but can occur as early as five days. TB-associated IRIS most commonly presents with fever and clinical deterioration of pre-existing lymphadenopathy or respiratory disease. Several reports suggest that IRIS is more common if ART is started early in the course of TB treatment and if the patient has a low CD4+ T-cell count. Most cases resolve without any intervention and ART can be safely continued. Serious reactions such as tracheal compression due to massive adenopathy may require a short course of steroids (1–2 mg/kg of prednisolone) based on clinical judgement (Narita, 1998; Kumarasamy, 2004; Lawn, 2005).

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EXERCISE 9.2.1

CASE STUDIES

Case 1

A 36-year-old male presents with a four-week history of fever, cough, fatigue, poor appetite and a weight loss of 6 kg. He just tested positive for HIV in the voluntary counselling and testing (VCT) centre today and was referred to the clinic for further evaluation. He does not have any previous illnesses and is not on any medications.

He first injected drugs in 1999 and quit in 2003. He currently works as a motorcycle taxi driver and lives with his wife.

Physical exam:

Temp 39°C, HR 110 beats/min, BP 110/90 mmHg, RR 18/min, weight 44 kg

Head eye ear nose and throat (HEENT): oral thrush

Neck: multiple lymph nodes on the right side 1–2 cm in size

Lungs: scattered rales, no wheezing

Heart, abdomen: normal

Skin: no rashes

- 1) **What WHO clinical stage is the patient in?**
- 2) **What further evaluation would you do at this time?**
- 3) **What is the most probable diagnosis?**
- 4) **What further diagnostic evaluation would you do?**
- 5) **What is the diagnosis?**
- 6) **What do you treat first: TB or HIV?**
- 7) **Does the patient meet the criteria for initiating ART?**
- 8) **When will you start ART?**
- 9) **What ART regimen would you start?**

Case 2

A 24-year-old male is referred from the TB clinic after testing positive for HIV. He is on the third week of treatment for pulmonary TB and is tolerating the treatment well. His fever has resolved and he gained 2 kg since starting treatment. His cough is better but he still coughs at night.

His medical history is notable for chronic hepatitis B infection and one episode of herpes zoster two years ago. He smokes ½ pack of cigarettes a day. He does not drink alcohol. He still uses heroin twice a day, but has been trying to decrease the amount he uses each time.

Physical exam:

No significant abnormalities noted

Laboratory exam:

CBC: WBC 5600 cells/mm³ (25% lymphocytes), Hb 10 g/dl, platelets 155 000/μl

CD4 225 cells/mm³

ALT 76 IU/ml, AST 65 IU/ml

HCV positive, HBsAg positive

- 1) **Does the patient meet the criteria for initiating ART?**

- 2) **Does current injecting drug use disqualify the patient for ART?**

- 3) **When would you start ART in this patient?**

- 4) **Which ART regimen would you use?**

Case 3

A 20-year-old male patient returns to the clinic for routine follow up. He was started on ART with d4T/3TC/NVP six weeks ago. Baseline CD4 count was 105 cells/mm³. At four weeks he was feeling well without any symptoms and results of routine blood testing (complete blood count [CBC], ALT, AST) were normal. Today he complains of fever, cough with white sputum, and a 1 kg weight loss over the past 10 days.

He started injecting drugs when he was 14 years of age and was admitted to a rehabilitation centre four years ago. He was released from the centre six months ago and now lives with his family. He does not use drugs currently.

Physical exam:

Temp 38.0°C, RR 16/min, HR 88 beats/min, BP 120/76 mmHg

HEENT: no thrush

Neck: no lymphadenopathy

Lungs: rales and wheezing on the upper left side

Heart: regular rhythm without murmurs

Abdomen: normal

Skin: no rashes

Chest X-ray: left upper lobe infiltrate

Sputum AFB: positive

- 1) **What is the diagnosis?**

- 2) **Do these findings indicate failure of the ART regimen?**

- 3) **The patient is started on rifampicin, isoniazid, pyrazinamide and ethambutol (RHZE) for TB. Will you stop the ART?**

- 4) **Will you change the ART regimen?**

CASE STUDIES: ANSWERS AND NOTES

Case 1

1) What WHO clinical stage is the patient in?

Clinical stage 3: weight loss >10% and oral thrush

2) What further evaluation would you do at this time?

Routine laboratory tests, chest X-ray, sputum for acid-fast bacilli (AFB), CD4 count (if available)

Results of laboratory testing:

CBC: WBC 3600 (25% lymphocytes)

Haematocrit 31%, Hb 9.2 g/dl, platelets 135 000/ μ l

CD4: 95 cells/ mm^3

ALT 46 IU/ml, AST 50 IU/ml

HCV positive, HBsAg negative

AFB x 3: negative

Chest X-ray: Right upper lobe infiltrates and interstitial infiltrate throughout

3) What is the most probable diagnosis?

Although the sputum is AFB negative, the most likely diagnosis is TB. The interstitial infiltrate on CXR is commonly seen with miliary TB, in which tubercle bacilli spread through the blood and the sputum is usually negative for AFB. The differential diagnosis would also include PCP and bacterial pneumonia. Less common causes would be viral pneumonia, fungal pneumonia, and *Mycobacterium avium* complex (MAC).

4) What further diagnostic evaluation would you do?

Rule out TB first: a repeat AFB would be reasonable. If AFB not found in the sputum, do a lymph node aspirate or biopsy. Sputum staining for bacteria, PCP and fungi should be done, if available. Cultures may also be helpful, although the results take longer.

Result: Aspiration of a cervical lymph node is positive for AFB.

5) What is the diagnosis?

TB lymphadenitis. TB is presumably causing the pulmonary disease as well.

6) What is the WHO clinical stage of the patient?

Extrapulmonary TB indicates WHO clinical stage 4.

7) What do you treat first: the TB or the HIV?

Start TB treatment first and consider ART when indicated.

8) Does the patient fulfil the criteria for ART?

Yes, WHO stage 4 and CD4 count 95 cells/mm³.

9) When will you start ART?

Between 2 and 8 weeks, as soon as the patient tolerates the TB treatment.

10) What ART would you start?

Preferred regimen: 2 NRTI + EFV

Other options: 2 NRTI + NVP, 3 NRTI

Case 2**1) Does the patient meet the criteria for initiating ART?**

Yes, clinical stage 3 (pulmonary TB) and CD4 count <350 cells/mm³

2) Does current injecting drug use disqualify the patient for ART?

No, active drug use is not a reason to deny care or ART.

However, the patient should be referred for counselling and drug treatment, where available.

Drug use can be associated with decreased adherence: active IDUs should be carefully counselled and monitored for adherence.

3) When would you start ART in this patient?

After 8 weeks, when the intensive phase of TB treatment is completed.

4) What ART regimen would you use?

If the patient continues on rifampicin:

- ◆ EFV-based regimens preferred
- ◆ NVP or triple NRTI regimens can be given, but monitor closely for hepatic toxicity if NVP used

If the patient continues on isoniazid and ethambutol:

- ◆ EFV or NVP regimens can be given

NOTE: The patient has high risk for hepatic toxicity due to chronic HBV, baseline elevated ALT, and use of TB drugs. Check ALT at 8 weeks before starting ART and follow closely.

Case 3

1) What is the diagnosis?

Active pulmonary TB.

2) Is this failure of the ART regimen?

No, development of active pulmonary TB while on ART does not indicate treatment failure and is common in the first six months of treatment.

3) The patient is started on RHZE for TB. Will you stop the ART?

NO! DO NOT STOP THE ART! You should continue ART while treating TB.

4) Will you change the ART regimen?

Concerns about NVP use with rifampin.

Preferred regimen is 2 NRTI + EFV, if available.

Other options: 3 NRTI or continue 2 NRTI + NVP.

If NVP continued: monitor closely for hepatic toxicity.

Presentation 9.1: HIV/HCV and HIV/HBV coinfections

Viral hepatitis coinfection in HIV-infected IDUs

Session objectives

Understand

- The epidemiology and background of HCV/HIV and HBV/HIV coinfection
- The influence of viral hepatitis on HIV progression
- The influence of HIV on progression of viral hepatitis
- Coinfection
- Treatment of HIV in viral hepatitis coinfection
- Treatment of viral hepatitis in HIV coinfection
- Future treatment of viral hepatitis in the presence of HIV infection

Hepatitis C coinfection

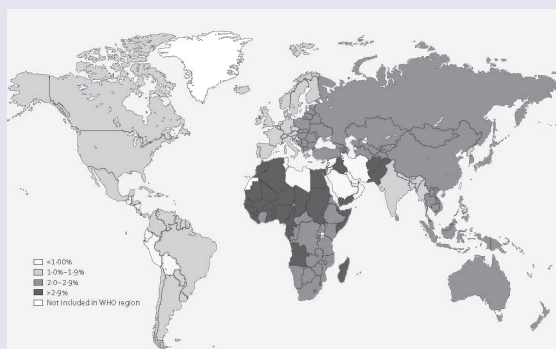
Management of hepatitis C in HIV-coinfected IDUs

Epidemiology of HCV

- 170 million people have hepatitis C worldwide
- Between 5% and 60% of HIV-positive individuals worldwide are HCV antibody positive (depending on the country)
- Over 90% of HIV-infected IDUs are also HCV-positive
- Transmitted by:
 - ◆ Blood-to-blood contact
 - ◆ Blood products (unscreened) such as transfusions
 - ◆ Not commonly spread via sexual contact except (potentially) in setting of HIV/HCV coinfection in men who have sex with men (MSM) especially with sexually transmitted infections (STIs)
 - ◆ Rarely mother-to-child except in setting of HIV/HCV coinfection [19% HIV/HCV versus 3.5% HCV]

Epidemiology

Prevalence of HCV worldwide

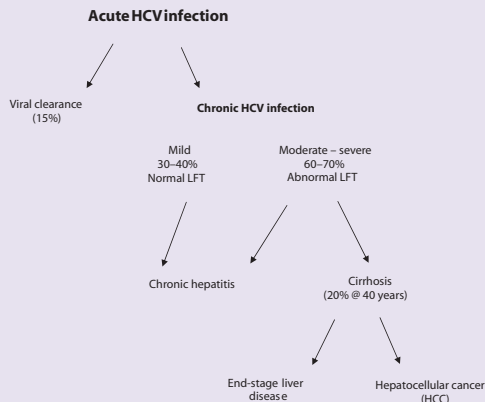


Source: Aceijas C, Rhodes T. *International Journal on Drug Policy*, 2007.

Background: HCV virus

- RNA flavivirus similar to dengue and Japanese encephalitis virus
- RNA viruses (such as HIV) are more prone to mutate than DNA viruses (such as HBV) and therefore often harder to treat
- Exists as many different variants during infection (quasispecies)
- 9 genotypes (subtypes), distribution varies
 - ◆ Genotypes 1, 2, 3 → Western countries and East Asia
 - ◆ Genotype 4 → Middle East and Central Africa
 - ◆ Genotypes 5, 6 → South Africa and South-East Asia

Background: natural history HCV monoinfection



Effect of HCV on HIV progression

- Limited long-term effect on HIV-associated mortality when CD4 count, age and HIV treatment taken into account
 - ◆ HCV/HIV coinfectd individuals may do worse than others many as more likely to be IDUs
- Increased LFT abnormalities following initiation of ARV (possibly immune, viral, toxicity)
- Liver-associated mortality increased in HIV/HCV coinfection
- Infection with multiple HCV genotypes may increase progression of HIV disease

Coinfection: HIV and HCV

Impact of HCV on HIV disease progression (EuroSIDA study: 33% HCV+, 1960/5957)

	Univariate	Multivariate
New AIDS illness	1.18 (1.03–1.35)	0.78 (0.62–0.98)
Any death	1.79 (1.56–2.06)	1.80 (1.44–2.25)
New AIDS/death	1.44 (1.29–1.60)	1.06 (0.89–1.28)
Liver disease-related death	10.02 (6.17–16.27)	12.31 (6.77–2.41)

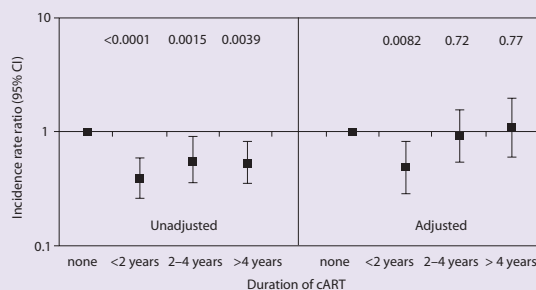
Source: Rockstroh JK et al; EuroSIDA Study Group. *Journal of Infectious Diseases*, 2005.

Effect of HIV on HCV progression

- Increased progression to cirrhosis [at 10 years HIV-uninfected 2.6% versus 14.9% HIV-infected]
- Increased liver failure, hepatocellular carcinoma (HCC) increased risk 6x to 11x in HIV coinfectd
- Factors associated with progression of liver disease in HCV/HIV coinfection are:
 - ◆ Heavy alcohol (ethanol) intake (>50 g/day) [some studies]
 - ◆ Uncontrolled plasma HIV RNA
 - ◆ Low CD4 count [some studies]
 - ◆ Increased quasispecies variability
 - ◆ Occult HBV infection (hepatitis B infection that is undetectable)
- Effective ART improves outcome of HCV disease [especially if suppresses plasma HIV RNA]

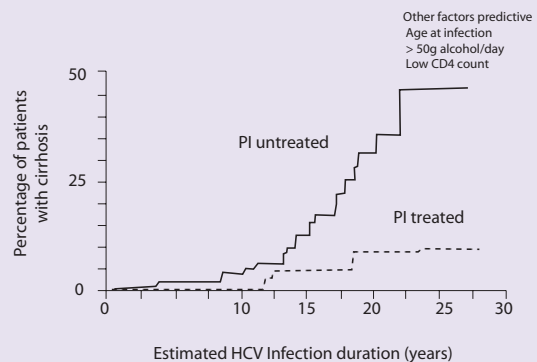
Coinfection: HIV and HCV

Impact of ART on liver disease mortality (EuroSIDA)



Source: Mocroft A et al; EuroSIDA Study Group. *AIDS Research and Human Retroviruses*, 2005.

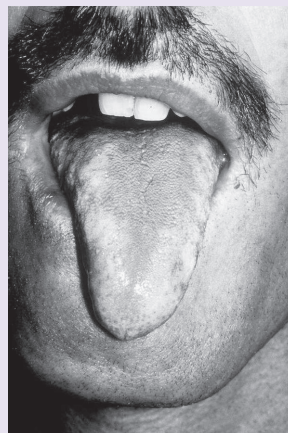
HCV/HIV coinfection: impact of ART



Source: Benhamou Y et al. *Hepatology*, 2001.

Mr NS – 1

- Mr NS, age 24 years, married man, presents after wife found to HIV-infected: prevention of mother-to-child transmission (PMTCT) programme
- Well, past five years and occasional current IDU (heroin x 1/week), alcohol twice weekly
- Recent weight loss 8 kg
- Examination: weight 56 kg, no fever, no peripheral signs of chronic liver disease, liver edge palpable

**Mr NS – 2**

- HIV antibody test positive
- WCC 1000 cells/mm³
- Hb 11 g/dl
- Platelets 43000/μl
- ALT 50 IU/ml
- What further investigations, advice, treatment should be considered?

Mr NS – 3

- WHO stage III
- HCVAb positive
- HBsAg negative; HBcAb positive
- Likely HCV infection, no evidence of HBV
- Management?

Mr NS – 4

- Cease alcohol
- Consider treatment for heroin addiction (e.g. methadone)
- Safe injection advice/education
- ART
 - ◆ AZT/3TC/EFV

Mr NS – 5

- Advice about symptoms of hepatotoxicity
 - ◆ Nausea and vomiting
 - ◆ Dark urine and jaundice
- At one-month follow up:
 - ◆ Feels well
 - ◆ Gains 5 kg, non-tender liver
 - ◆ Repeat Hb 11.4 g/dl; platelets 170 000 μl; WCC 2000 cells/mm³
 - ◆ ALT 160 IU/ml
- Management/advice?

Mr NS – 6

- Continue and monitor
 - ◆ Initial hepatotoxicity commonly transient
- Future access to HCV treatment to be reconsidered

Hepatitis C: dos and don'ts

DO:

- Vaccinate against hepatitis B and A, if required
- Regular health check-ups
- Stop or reduce alcohol intake
- Protect from *re-infection*; having hepatitis C antibodies will *not* protect from re-infection
- Eat a balanced diet of fresh vegetables, fruits, beans, whole grains and lean meats; a healthy balance of protein in the diet
- Drink lots of fluids
- Exercise regularly
- Make a stress reduction plan

AVOID:

- Drinking alcohol
- Taking large amounts of acetaminophen (paracetamol)
- Acetaminophen and alcohol together can cause severe liver damage
- Breathing in pollutants, chemicals, cleaning products, fumes from paint, paint thinners, chemical solvents, spray adhesives, insect sprays and cleaners can be harmful to the liver
- Foods with high salt, sugar or fat content
- Fatty foods
- High doses of vitamins A, D, E or K
- Taking iron supplements unless advised by the doctor

Treatment of HIV in HCV coinfection – 1

- Abnormal LFT is common and often occur early and are asymptomatic so important to monitor symptoms and LFT
- Severe hepatotoxicity (symptoms +/- or ALT >5 x upper limit of normal [ULN]) USUALLY requires stopping ART
- Monitoring during initiation and treatment
 - ◆ HCV test and LFT prior to treatment
 - ◆ Question about symptoms, regular (every 3 months) + LFT during treatment
 - ◆ If NVP-containing ART, use with caution
 - Women have increased risk of reaction (rash without fever; fever and rash; fever, rash and hepatitis)

Treatment of HIV in HCV coinfection – 2

Choice of ART regimen

- Depends on individual, but avoid hepatotoxic drugs
- NNTRI-based regimens
 - ◆ Caution with NVP
- NTRI
 - ◆ Can cause hepatic steatosis (fatty liver)
 - ◆ AVOID ddI and d4T with RBV
- PI-based regimens
 - ◆ Can cause liver injury (especially high-dose RTV)

Management of hepatotoxicity in HCV/HIV coinfecting individuals

- Overall rate 10%
 - ◆ Risk factors > 5 x ULN enzymes: AST =/or ALT >1.25 ULN at ARV commencement
 - ◆ Platelet count < 99 000/ μ l
 - ◆ Other hepatotoxic medications
 - ◆ Creatinine >1.5 ULN
- Mortality reduced in ART treated despite hepatotoxicity
- Educate patient about symptoms of hepatotoxicity: jaundice; darkening of urine; right upper quadrant pain; nausea, anorexia, pruritus or fatigue
- Mild initial abnormalities of LFT **NOT** indication to stop ART, rather to monitor

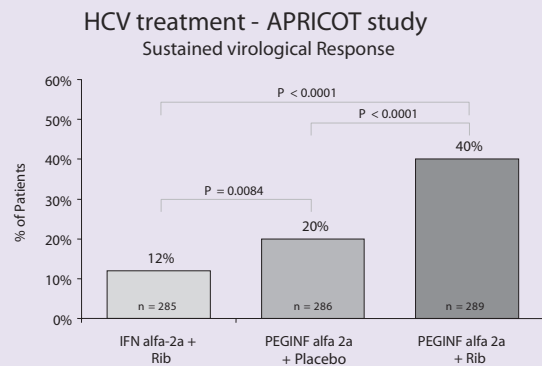
Hepatitis C terminology in treatment response

Acronym	Refers to	Meaning
EVR	Early virological response	Usually a reduction in viral load 12 weeks into treatment, though this varies by level of reduction and timing
ETR	End-of-treatment response	Undetectable HCV RNA at the end of treatment
SVR	Sustained virological response	Undetectable HCV RNA at 24 weeks after completion of treatment. Obtaining a sustained virological response is often referred to as a "cure"
NR	Non-responder	No significant reduction in HCV RNA levels (<2 log.) after a specified interval of treatment (usually 24 weeks), or no significant decrease in HCV RNA, but never becomes HCV RNA undetectable during treatment. Some non-responders may have improved liver histology after treatment

Treatment of HCV in HIV coinfection

- Treatment is expensive which limits accessibility
- Current preferred treatment regimen:
 - ◆ Pegylated (PEG-IFN) interferon (SC weekly injection) + RBV 800 mg (PO daily) for 48 weeks [RBV weight-based in genotype 1]
- Effectiveness (SVR)
 - ◆ Sustained viral clearance in 27% interferon and **40% PEG/RBV overall**, and up to 73% in genotype non-1 PEG/RBV
- Which virus to treat first currently uncertain – guidelines say:
 - ◆ Treat HIV first if CD4 <200 cells/mm³
 - ◆ Treat HCV first if CD4 >350 cells/mm³, significantly improved outcome if ART and plasma HIV RNA suppressed [consider concurrent ART]
- New treatments on the horizon, **HCV protease inhibitors**

HCV treatment - APRICOT study sustained virological response



Source: Torriani FJ et al; APRICOT Study Group. *New England Journal of Medicine*, 2004.

Treatment of HCV in HIV coinfection – 1

- Reinfection (infection with new virus)
 - ◆ Limited data, probably uncommon
 - ◆ Prevent with HCV transmission prevention interventions (needle-syringe programmes, etc.)
- Relapse (return of original virus)
 - ◆ Almost always happens in first six months after treatment
 - ◆ 10% in genotype 1
 - ◆ 2% in genotypes 2 and 3

Treatment of HCV in HIV coinfection – 2

- Treatment is difficult but effective to clear/cure HCV especially in favourable genotypes.
- Side-effects:
 - ◆ IFN:
 - Depression (treat aggressively with selective serotonin reuptake inhibitors [SSRI])
 - Flu-like symptoms (treat with paracetamol)
 - Neutropenia (reduce dose if <0.75, <0.5 may require cessation of treatment)
 - ◆ RBV
 - Haemolytic anaemia (may require dose reduction if symptomatic)
 - DO NOT use with ddl plus/minus d4T in liver failure

Treatment of HCV in HIV coinfection – 3

- Substance use treatment
 - ◆ Needs to be evidence-based (e.g. OST)
- Prevention of pregnancy
 - ◆ Treatment of HCV is teratogenic (for both males and females) therefore two forms of contraception should be used (barrier and oral contraceptive pill)
 - ◆ No pregnancy should occur before ~6 months of stopping RBV

Conclusion

- HCV/HIV coinfection is very common in HIV-infected IDUs
- Test for HCV plus LFT prior to HIV treatment if possible
- Treat HIV in all as indicated (WHO 3 or 4)
- Avoid alcohol, treat substance use
- Advise use of sterile injecting equipment
- Use NVP in HIV treatment with care
- Asymptomatic change in LFT not an indication to cease ARVs
- Monitor LFT during HIV treatment
- If possible consider HCV treatment, currently PEG/RBV, future HCV protease inhibitors

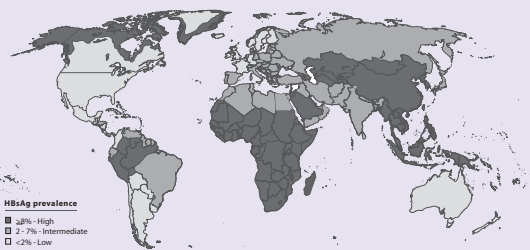
Hepatitis B coinfection

Management of hepatitis B in HIV coinfecting IDUs

Epidemiology

- 400 million infected worldwide, with 500 000 deaths each year as a result
- Endemic in Asia and Africa (10–15% chronically infected)
- Low prevalence in western Europe, North America and Australia
- Transmission
 - ◆ Mother-to-child (5% chance)
 - ◆ Close contact between infants, mother (perinatal)
 - ◆ Unprotected sex
 - ◆ Blood-to-blood (sharing injecting equipment, unsterilized transfusions)
- Chronic infection very common in infancy, very uncommon in adult acute infection
- Epidemiology of HBV/HIV less well understood, though IDUs in Asia are at high risk

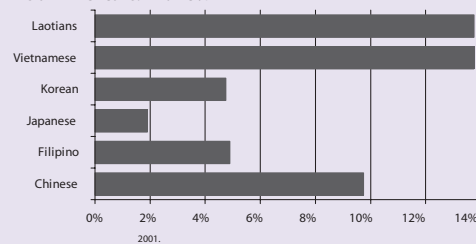
Geographical distribution of chronic HBV infection



Source: World Health Organization. *Hepatitis B*. Geneva, WHO, Department of Communicable Diseases Surveillance and Response, 2002. http://www.who.int/csr/disease/hepatitis/HepatitisB_who_dscrlyo2002_2.pdf
World Health Organization, 2002.

Hepatitis B prevalence

- Overall U.S. prevalence: 0.3%
- Asian Americans: ~10-13%



Son D. *Asian American and Pacific Islander Journal of Health*, 2001. Slide courtesy of Robert Gish, MD

Background: Hepatitis B virus

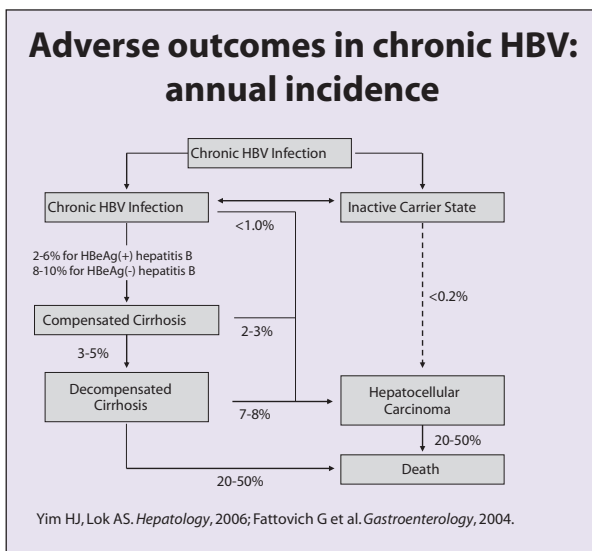
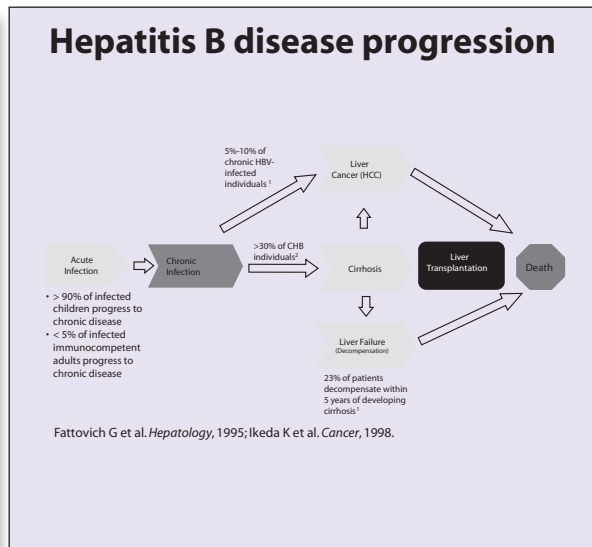
- DNA hepadnavirus
- Infects liver cells (hepatocytes)
- Liver damage is from immune injury
- Eight hepatitis B genotypes: may relate to hepatocellular carcinoma (HCC) (including subtype Ba) or response to INF
 - ◆ A is pandemic (USA, Africa, W. Europe)
 - ◆ B and C are found in Asia
 - ◆ D in Southern Europe, India and Africa
 - ◆ E in West Africa
 - ◆ F in the USA, Central and South America
 - ◆ G in the USA and France
 - ◆ H unclear

Background: HBV markers

Marker	Full form	Indicates
HBsAg	Hepatitis B surface antigen	Current infection with hepatitis B (a carrier)
HBsAb	Hepatitis B surface antibody	Immunoprotection against hepatitis from either vaccination or previous exposure
HBcAb	Hepatitis B core antibody	Previous exposure to hepatitis B
HBeAg	Hepatitis B e antigen	Marker of active replication/active disease
HBeAb	Hepatitis B e antibody	Marker of inactive disease, so called "e seroconversion"
HBV DNA	Hepatitis B DNA	Presence indicates active replication and disease. Amount of DNA is "HBV viral load"

Background: HBV markers

Test combination	Results	Interpretation
HBsAg HBcAb HBsAb	- - -	Susceptible to hepatitis B
HBsAg HBcAb HBsAb	- + +	Past history of HBV with current immunoprotection
HBsAg HBcAb HBsAb	- - +	Immune due to hepatitis B vaccination
HBsAg HBcAb HBsAb	- + -	Past history of HBV infection



- ### Effect of HBV on HIV progression
- Early studies suggested HBV may increase HIV progression BUT following ART now considered that HBV infection does not accelerate HIV progression
 - Acute post-ART flare 10–15% with reported mortality; risk CD4 count <200 cells/mm³
 - Viral resistance is increased in HBV/HIV coinfecting individuals, possible contributing factors:
 - ◆ Higher HBV viral load difficulty suppressing
 - ◆ Monotherapy
 - ◆ Interrupted treatment due to hepatotoxicity

- ### Effect of HBV on HIV progression
- HIV results in:
 - ◆ Higher HBV viral load
 - ◆ Reduced HBeAg seroconversion
 - ◆ Increased liver fibrosis and cirrhosis
 - ◆ No change in liver cancer rates
 - ◆ Increased liver-related mortality
 - Effective ART can reduce progression, but care needs to be taken
 - ◆ Resistance
 - ◆ Immune flares: early
 - ◆ Withdrawal hepatitis when cessation of 3TC and/or TDF
 - ◆ Drug toxicity with NVP (early) and RTV

- ### Mr LM – 1
- 32-year-old male IDU
 - Injects heroin/methamphetamine, often mixing these with diazepam, less drug use recently
 - Began injecting at 19 years, spent four years in prison
 - Diagnosed HIV-positive seven years ago, during prison sentence
 - Abnormal liver function test: ALT 60 IU/ml
 - Now shingles, oral candidiasis
 - Management?

Mr LM – 2

- Initial tests
 - ◆ WCC 900 cells/mm³
 - ◆ CD4 count 40 cells/mm³, ALT 130 IU/ml, HBsAg positive, HCVAb negative
- Commenced on d4T/3TC/NVP
- Two weeks later, developed nausea, fever, right upper quadrant tenderness
- Continues to inject occasionally
- Response?
- ALT = 957 IU/ml?
- Options?

Mr LM – 3

- Possibilities:
 - ◆ Immune restoration
 - ◆ Hepatotoxicity (e.g. NVP)
 - ◆ Superinfection with HCV
- Probably immune reconstitution inflammatory syndrome (IRIS) from hepatitis B
 - ◆ He has a low CD4 count → increased risk
 - ◆ Known HBsAg positive
 - ◆ Likely high viral load
- Management options:
 - ◆ Cease ART
 - ◆ Cease ART except 3TC +/- other HBV active agent (e.g. TDF, entecavir)
 - ◆ Ideally, commence 3TC before HIV treatment
 - ◆ Monitor symptoms and recommence ART when normalized
 - d4T/3TC/EFV

Treatment of HIV in HBV coinfection

- Hepatotoxicity
 - ◆ Does occur and causes are similar to HCV/HIV coinfection
 - Immune
 - Hepatotoxicity
- Choice of ART regimen
 - ◆ Use ARVs with activity against hepatitis B (3TC, TDF) possibly better if combined improved efficacy and resistance (no RCT data yet)
- Monitoring during initiation and treatment
 - ◆ Test for hepatitis B (at least HBsAg) and do LFT prior to ART commencement
 - ◆ Monitor ALT regularly (every three months in the first year) during HIV treatment

Prevention of HBV in HIV infection

- Prevention
 - ◆ Safe sex (barrier protection)
 - ◆ Sterile injecting equipment
 - ◆ Vaccination of all IDUs (if no existing immunoprotection)
 - 0, 1 and 6 months or 0, 1, 2 and 12 months
 - Double dose (40 µg/ dose); repeat post-ART if no response
 - Need CD4 count > 200 cells/mm³ for immune response – CONSIDER delay until immune recovery

Currently available treatment of HBV – 1

- **3TC 300 mg/day**
 - ◆ Cheapest, most prone to resistance (usually in 1–4 years), also used in HIV treatment
 - ◆ Reduces viral load in 85% of people
 - ◆ Few side-effects
- **TDF 300 mg/day**
 - ◆ Low resistance, also used in HIV treatment
 - ◆ Effective in 3TC-resistant hepatitis B
 - ◆ Well tolerated, may cause renal dysfunction (rare)
- **Emtricitabine (FTC) 200 mg/day**
 - ◆ Cross-resistance with 3TC
 - ◆ Reduces HBV viral load equivalent to 3TC
 - ◆ Side-effects include rash, skin pigmentation

Currently available treatment of HBV – 2

- **Adefovir divipoxil 10 mg/day**
 - ◆ Reduction HBV DNA substantial but slow
 - ◆ Not effective in HIV treatment at this dose
 - ◆ Renal toxicity at increased doses
 - ◆ Resistance develops slowly but not cross-resistant 3TC, reduced in combination with 3TC
- **Entecavir 0.5 mg/day or 1 mg/day in 3TC resistance**
 - ◆ Low rates of resistance, no effect HIV
 - ◆ Potent HBV suppression
- **PEG-IFN**
 - ◆ Very expensive
 - ◆ Most effective treatment (weekly SC injections for 48 weeks)
 - ◆ Low resistance? But many side-effects especially in cirrhotics
 - ◆ No advantage in combination with 3TC

Treatment of HBV in HIV coinfection

- **In individuals requiring HIV treatment and HBV treatment:**
 - ◆ ARVs with hepatitis B activity should be included in the regimen.
 - If only one agent available use 3TC. 3TC can be used alone but resistance will develop.
 - If other single agents, use TDF [better resistance profile].
 - If two agents possible, then 3TC plus TDF.
- **In individuals requiring HIV treatment and not HBV treatment:**
 - ◆ Type of ART regimen should be determined by normal indications.
 - ◆ If hepatitis B replication is under control (HBV DNA <4 log¹⁰ copies/ml), ART does not have to contain agents with dual activity.
- **In individuals with cirrhosis:**
 - ◆ These patients are at risk of hepatic decompensation (failure) when ART is initiated, particularly if CD4 count is low and HBV viral load is high.
 - ◆ Therefore use combination (e.g. 3TC + TDF) initially to reduce HBV viral load before commencement of full ART if possible.

Treatment of HBV in HIV coinfection

- **In individuals requiring HBV treatment and not HIV treatment:**
 - ◆ Delay treatment
 - ◆ Use pegylated interferon (PEG-IFN) or a non-ART agent to avoid resistance developing to the agent (e.g. adefovir [ADV], entecavir)
- **In individuals with 3TC resistance:**
 - ◆ Suspect if HBV viral load increases by 1 log¹⁰ copies/ml or recurrent elevation of ALT after suppression
 - ◆ Add TDF to regimen if only using 3TC. Can also add ADV or entecavir (if ART is not necessary)

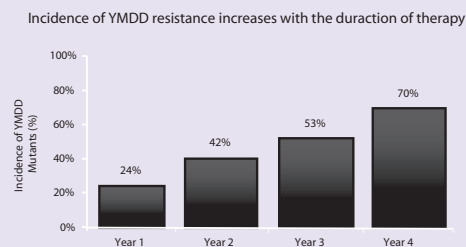
Treatment of HBV in HIV coinfection: effectiveness

- **HBV DNA level**
 - ◆ This is called viral load and is the best way to monitor effectiveness of treatment. It is also **the most expensive**.
 - ◆ 3TC reduces viral load by almost 3–5 log¹⁰ copies/ml after one year of treatment.
 - ◆ ADV reduces viral load by 4 log¹⁰ copies/ml after one year of treatment.
 - ◆ TDF reduces viral load by 5 log¹⁰ copies/ml regardless of resistance to 3TC.
- **HBeAg seroconversion**
 - ◆ Development of HBeAb is a result of treatment which indicates control of replication.
 - ◆ Only a minority of individuals on treatment will obtain HBeAg seroconversion: 3TC 25%; ADV 30%; PEG-IFN 30%.
- **ALT levels**
 - ◆ Cheapest, but can be difficult to interpret
 - ◆ Decreased viral load = decreased ALT
 - ◆ Decreased ALT levels = better histology (on liver biopsy) during therapy
 - ◆ ALT can rise during:
 - Control of viral replication (due to restoration of immune function)
 - Liver toxicity from drug therapy
 - Immune flares

HBV treatment: resistance

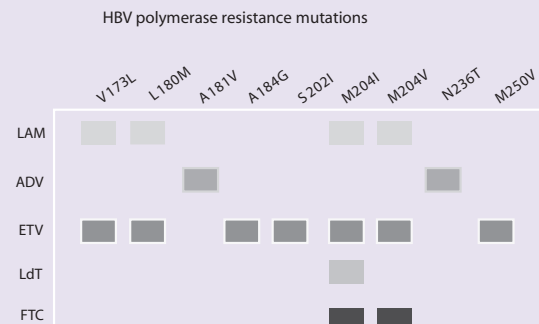
- Most common with 3TC – 70% by four years
- Least common with TDF – rare single reports
- Dual therapy (ADV + 3TC) results in less risk of mutations—little data as yet
- Resistance mutations can be identified by analysis of HBV DNA, but this is expensive, recurrent HBV DNA, flare of ALT also occurs in some

Development of resistance to 3TC



Source: Lai CL et al. *Clinical Infectious Diseases*, 2003.

Coinfection: HIV and HBV



Source: Locarnini S et al. *Antiviral Therapy*, 2004.

Feasibility of HBV treatment in resource-limited settings

- Can be difficult to treat HBV in HIV coinfection in resource-limited areas, therefore:
 - ◆ Vaccinate for HBV
 - ◆ Stabilize drug use (e.g. OST)
 - ◆ Advise reduction or cessation of alcohol use
 - ◆ Delay HBV treatment until commencement of ART unless cirrhotic and low CD4 count
 - ◆ Use ARVs with HBV suppression activity in the treatment of HIV
 - ◆ DO NOT withdraw 3TC without consideration of HBV disease (risk of flares)

Conclusion

- HBV is very common in HIV-infected IDUs.
- All HIV-positive IDUs should be screened for HBV.
- HIV-positive IDUs should be vaccinated against HBV if not immune.
- Treatment for HBV should be withheld until indication to treat HIV.
- HIV treatment regimens in the context of HBV should include those ARVs that suppress HBV.
- ALT should be monitored during HIV/HBV treatment.
- Combined 3TC/TDF should be considered in HIV/HBV coinfection and in 3TC resistance.

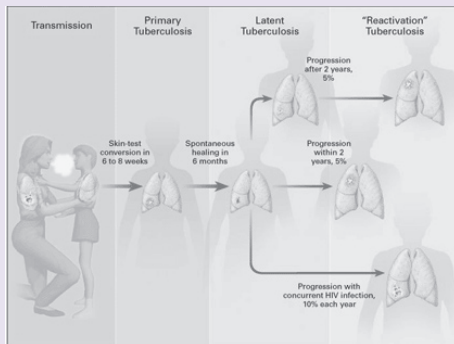
Presentation 9.2: Management of HIV/TB coinfection in IDUs

Management of HIV/TB coinfection in IDUs

Session objectives

- Describe the epidemiology of HIV/TB coinfection in South-East Asia
- Use the WHO guidelines to prescribe co-trimoxazole (CTX) preventive treatment
- Describe care and treatment for HIV-infected IDUs with active TB
- Prescribe appropriate ARVs for HIV-infected IDUs with active TB

Tuberculosis: pathogenesis



Source: Small PM, Fujiwara PI. *New England Journal of Medicine*, 2001

TB transmission

- Transmitted by inhalation of infectious droplet nuclei from infected person
- Sputum smear positive (SS+) pulmonary TB cases account for most TB transmission in the community
- Most TB infections (90% in non-HIV infected people) remain latent
- PLWHA and IDUs have higher rates of progression to active TB or reactivation of latent infection

Incidence of active TB in persons with positive tuberculin skin test

Risk factor	TB cases/1000 person-years
Latent TB infection (>1 year)	1.6
IDU HIV-negative	10
Recent TB infection (<1 year)	12.9
IDU HIV-positive	76
HIV/AIDS	35–162

Source: American Thoracic Society/Centers for Disease Control and Prevention. *American Journal of Respiratory and Critical Care Medicine*, 2000.

TB/HIV coinfection

- TB is the most common opportunistic infection (OI) among HIV-infected patients in developing countries
- IDUs have a higher incidence of active TB infection, regardless of HIV status
- The manifestations of TB may be different in PLWHA
- WHO recommends screening:
 - ◆ ALL TB patients for HIV (voluntary counselling and testing [VCT])
 - ◆ ALL HIV patients for TB infection

Prevalence of OIs among persons with AIDS, Thailand (2 series)

	Prevalence
• Tuberculosis	29–37%
• Cryptococcosis	19–38%
• Wasting syndrome	8–28%
• <i>P. jiroveci</i> pneumonia (PCP)	5–20%
• Bacterial pneumonia	4%
• Oesophageal candidiasis	3–6%
• <i>Penicillium marneffeii</i> infection	3%
• Toxoplasmosis	2–3%
• Cryptosporidiosis	1–2%

Sources: Chariyalertsak S et al. *Clinical Infectious Diseases*, 2001; Tansuphasawadikul S et al. *Journal of Acquired Immune Deficiency Syndromes*, 1999.

OI distribution in 100 HIV/AIDS patients at Tropical Disease Hospital (HCMC, Viet Nam) – 2000

• Oral thrush	53%
• Tuberculosis	37%
• Wasting syndrome	34%
• Respiratory infections	13%
• Cryptococcosis	9%
• Penicilliosis	7%
• PCP	5%
• Septicaemia	4%

Source: Louie JK et al. *International Journal of STD and AIDS*, 2004.

Causes of respiratory infections among 295 PLWHAs in Cambodia

TB	39%
PCP	30%
Bacteria	16%
Mycosis	6%
Non-TB mycobacteria	5%
Strongyloides	4.7%
Cancer	0.3%

Source: Agence Nationale de Recherche sur le SIDA (ANRS) 1260, 2004.

Pneumocystis jiroveci pneumonia (PCP)

- Common cause of respiratory infections in SE Asia
- Increased risk with CD4 count <200 cells/mm³
- Prevention: CTX 960 mg once a day
- WHO criteria for CTX prophylaxis in adults:
 - ◆ No CD4 testing: WHO clinical stages 2,3,4
 - ◆ CD4 testing available:
 - WHO clinical stages 3-4
 - CD4 count <200 cells/mm³ (for PCP and toxoplasmosis)

2006 WHO guidelines for CTX prophylaxis in infants and children

HIV-EXPOSED INFANTS AND CHILDREN ^a	SITUATION		
	INFANTS AND CHILDREN CONFIRMED ^b TO BE LIVING WITH HIV		
	<1 YEAR	1–4 YEARS	≥ 5 YEARS
CTX prophylaxis is universally indicated, starting at four to six weeks after birth and maintained until cessation of risk of HIV infection	CTX prophylaxis is indicated regardless of CD4 percentage or clinical status	WHO clinical stages 2, 3 and 4 regardless of CD4 percentage OR Any WHO stage and CD4 <25%	Follow adult recommendations
Universal option prophylaxis for all infants and children born to mothers confirmed or suspected of living with HIV. This strategy may be considered in settings with high prevalence of HIV high infant mortality due to infectious diseases and limited health infrastructure [C-IV].			

a. Until six weeks after complete cessation of breastfeeding and infection can be excluded

b. Confirmation by virological testing among children <18 months

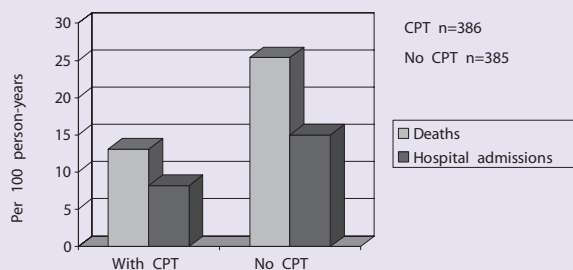
c. Once started, continue CTX until 5 years of age

Source: WHO, 2006.

CTX prevents many infections in PLWHA:

Infection	Pathogen
Pneumonia	<i>Pneumocystis jiroveci</i> <i>Strep. pneumoniae</i> <i>Haemophilus influenzae</i>
Bacteraemias	<i>Salmonella</i> <i>Strep. pneumoniae</i>
Encephalitis	<i>Toxoplasma gondii</i>
Skin infections	<i>Staph. and Strep. species</i>
Protozoa	Malaria

CTX preventive treatment (CPT) significantly decreases mortality and hospital admissions in HIV-associated active TB



Source: Wiktor SZ et al. *Lancet*, 1999.

PCP prophylaxis

- For patients allergic to CTX:
 - ◆ Dapsone: adults 100 mg once a day
- When can CTX be stopped?
 - ◆ Adults:
 - CD4 count >200–350 cells/mm³ after six months of ART
 - If no CD4 count available: on ART for one year with no new clinical stage 2, 3, or 4 events

Treatment for TB

- Latent TB infection
- Active TB infection
 - ◆ In patients on ART treatment
 - ◆ In patients not yet on ARV

Treatment of latent TB infection

- Latent TB infection is diagnosed by tuberculin skin testing (TST)
- Rule out active TB infection before treating latent infection to avoid drug resistance
- Prophylaxis has been shown to decrease active TB infection for up to three years
 - ◆ Refer to national TB programme guidelines
- Cautions: monitor for signs of hepatotoxicity
 - ◆ Add pyridoxine 25–50 mg/day to INH to prevent neuropathy
 - ◆ Be aware of interactions and cross-toxicities between ARV and TB drugs

Treatment of active TB infection

General principles:

- Treatment of TB in PLWHA is the same as in non-HIV-infected patients
- Follow national guidelines for TB treatment
- Usual regimens for pulmonary and extrapulmonary TB:
 - ◆ Two months intensive phase: *RHSZ* or *RHZE*
 - ◆ Consolidation phase: four months *RH* or six months *HE*
- Treatment for TB meningitis (9–12 months)

ART and TB

- HIV-infected persons with active TB will often be offered ART because those with pulmonary TB meet criteria for WHO stage 3 and those with extrapulmonary TB for WHO stage 4
- ART may be highly beneficial in these persons in reducing case-fatality rates in TB
- Patients already receiving ART may develop clinical TB
- *TB treatment should be initiated promptly regardless of the HIV serostatus*

Co-management of HIV and TB is challenging

- Drug interactions between rifampicin and several classes of ARVs
- High pill burden
- Adherence problems
- Drug toxicity
- Immune reconstitution inflammatory syndrome (IRIS)

TB and ARV: general principles

- **Treat TB first!** The patient should be tolerating TB therapy for at least two weeks before starting a new ART regimen.
- **Do not stop the ART!** – if the patient is already on ART before the diagnosis of TB
 - ◆ Be aware of the interactions between TB therapy and ARV drugs
 - ◆ Change the ART regimen if needed and available (i.e. change NVP to EFV)
- **Start ART!** Consider starting ART as soon as possible following WHO and national guidelines.

When to start ART in adults and adolescents with active TB disease

- Optimal timing of initiation of ART is not known.
- Case-fatality rates in patients with TB during the first two months of TB treatment are high.
- Where CD4 counts are not available, WHO recommends that ART be considered in all patients after the intensive phase of TB treatment.

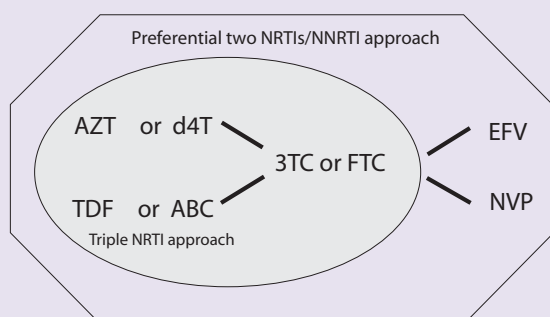
When to start ART in adults and adolescents with active TB disease: WHO 2006

CD4 count cells/mm ³	ART recommendations	ART timing after TB treatment started
<200	Recommend ART	2–8 weeks
200–350	Recommend ART	After 8 weeks
>350	Defer ART (1)	Re-evaluate at 8 weeks and after TB treatment completed
not available	Recommend ART (2)	2–8 weeks

Notes: (1) Consider ART if other non-TB stage 3-4 conditions are present.
(2) If clinically stable and responding to TB treatment, can defer ART until after TB treatment completed.

Source: WHO, 2006.

What ART to start? WHO 2006 recommendations



Source: WHO, 2006.

First-line ART regimens in the setting of TB treatment for adults and adolescents

- Preferred regimen: **2 NRTI + EFV**
 - ◆ Do not use in the first trimester of pregnancy
- Alternate regimen: **2 NRTI + NVP**
 - ◆ ↓ NVP levels with rifampicin
 - ◆ Do not use in women with CD4 count >250 cells/mm³
 - ◆ Monitor carefully for hepatotoxicity (ALT at 4, 8, 12 weeks)
- Triple NRTI option: **AZT + 3TC + (ABC or TDF)**
 - ◆ Safe for pregnant women, women with CD4 count >250 cells/mm³, hepatitis
 - ◆ Concern about lower efficacy than NNRTI-containing regimens

Active TB in adults and adolescents already on ART

Issues:

- Does a new diagnosis of TB in a patient on ART represent treatment failure?
- Do first-line regimens need to be changed?
- Do second-line regimens need to be changed?

Active TB in adults and adolescents already on ART

Does a new diagnosis of TB in a patient on ART represent treatment failure?

- TB in the first six months of ART is a common presentation of previously undiagnosed or sub-clinical TB.
- After six months, treatment failure can be assessed by CD4, viral load, or clinical criteria.
- Pulmonary TB alone after six months does not indicate treatment failure.
- Extrapulmonary or disseminated TB after six months may indicate treatment failure.

Active TB in adults and adolescents already on ART

Do first-line regimens need to be changed?

- EFV-based or triple-NRTI regimens can be continued.
- Options for NVP-based regimens:
 1. Switch to EFV-based or triple-NRTI regimen
 - Can switch back to NVP when rifampicin therapy completed
 2. Continue NVP-based regimen
 - Monitor closely for hepatotoxicity

Active TB in adults and adolescents already on ART

Do second-line regimens need to be changed?

- Unboosted PI cannot be taken with rifampicin due to decreased levels of the PI
- Options for second line:
 - ◆ 2 NRTI + LPV/RTV
 - ◆ 2 NRTI + SQV/RTV
- RTV + rifampicin have ↑ risk for hepatic toxicity: monitor clinical signs and ALT closely

Immune reconstitution inflammatory syndrome (IRIS)

- Paradoxical development of new signs and symptoms of OI, or worsening of symptoms of a previously treated OI after initiation of ART
- Usually occurs in the first 2–12 weeks of ART
- Occurs in up to 33% of TB patients who start ART
- Increased risk for IRIS if ART started soon after TB treatment or with low CD4 counts
- Symptoms of TB-IRIS include fever, lymphadenopathy, and worsening of respiratory disease

IRIS: treatment

- Rule out new or recurrent OI
- Continue ART unless symptoms are very severe or life-threatening
- IRIS will resolve in several weeks without specific treatment
- Treat symptoms as appropriate (e.g. NSAIDs or paracetamol for fever and pain)
- Severe symptoms can be treated with steroids
 - ◆ Prednisone 0.5–1.0 mg/kg/day for 1–2 weeks then taper

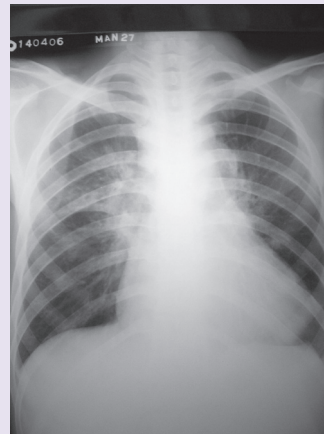
TB associated IRIS



TB patient with worsening lymph node enlargement and drainage after starting ART

Source: D Colby

TB IRIS



27-year-old male IDU in northern Viet Nam at month 5 of treatment for pulmonary TB. Presents after six weeks of ART with increased cough, fatigue and fever. Sputum AFB X 3 negative. Symptoms resolved after four weeks' treatment with diclofenac.

Source: D Colby

Conclusions

- TB and HIV are often found together: screen all IDU patients for both
- Recommend CTX prophylaxis to all HIV-positive TB patients
- Same TB treatment for HIV-infected and uninfected patients: follow national guidelines
- ART should be considered in all patients with TB/HIV coinfection
- Be aware of the interactions and overlapping toxicities of TB drugs and ART
- IRIS is common in TB patients after starting ART

Case study 1

A 36-year-old male presents with a four-week history of fever, cough, fatigue, poor appetite and a six kg weight loss. He just tested positive for HIV in the VCT today and was referred to the clinic for further evaluation. He does not have any previous illnesses and is not on any medications.

He first injected drugs in 1999 and quit in 2003. He currently works as a motorcycle taxi driver and lives with his wife.

Case study 1 (cont.)

Physical exam:

Temp 39, HR 110, BP 110/90, RR 18, weight 44 kg

HEENT: oral thrush

Neck: multiple lymph nodes on the right side 1–2 cm

Lungs: scattered rales, no wheezing

Heart, abdomen: normal

Skin: no rashes

Case study 1: right supraclavicular lymphadenopathy



Source: D Colby

Case study 1 (cont.)

Questions:

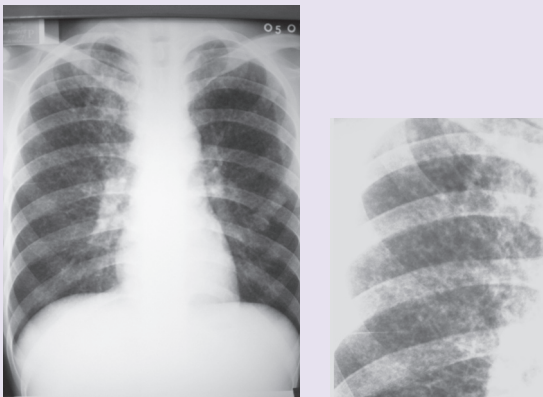
- 1) What WHO clinical stage is the patient in?
- 2) What further evaluation is required?

Case study 1 (cont.)

Results of laboratory testing:

CBC: WBC 3600 (25% lymphocytes)
 Haematocrit 31%, Hb 9.2, platelet 135 000
 CD4: 95 cells/mm³
 ALT 46 IU/ml, AST 50 IU/ml
 HCV positive, HBsAg negative
 AFB x 3 negative

Case study 1: CXR



Source: D Colby

Case study 1 (cont.)

Questions:

- 3) What is the most probable diagnosis?
- 4) What further diagnostic evaluation would you do?

Case study 1 (cont.)

Result: aspiration of a cervical lymph node is positive for AFB

- 5) What is the diagnosis?
- 6) What is the WHO clinical stage of the patient?

Case study 1: treatment

- 7) **What do you treat first: the TB or the HIV?**
 - ◆ Start TB treatment first and consider ART when indicated
- 8) **Does the patient fulfil criteria for starting ART?**
 - ◆ Yes, WHO stage 4 and CD4 count 95 cells/mm³
- 9) **When will you start ART?**
 - ◆ Between 2 and 8 weeks, as soon as the patient is tolerating TB treatment
- 10) **What ART would you start?**
 - ◆ Preferred regimen: 2 NRTI + EFV
 - ◆ Other options: 2 NRTI + NVP, 3 NRTI

Case study 2

A 24-year-old male patient is referred from the TB clinic after testing positive for HIV. He is in the third week of treatment for pulmonary TB and is tolerating the treatment well. His fever has resolved and he has gained 2 kg since starting treatment. His cough is better but he still coughs at night.

His medical history is notable for chronic HBV infection and one episode of herpes zoster two years ago. He smokes ½ pack of cigarettes a day. No alcohol. He still uses heroin twice a day, but has been trying to decrease the amount he uses each time.

Case study 2 (cont.)

Physical examination: no significant abnormalities

Laboratory examination:

CBC: WBC 5600 (25% lymph), Hb 10, platelet 155 000
 CD4 225 cells/mm³
 ALT 76 IU/ml, AST 65 IU/ml
 HCV positive, HBsAg positive

Case study 2 (cont.)

1) Does the patient fulfil criteria for starting ART?

- ◆ Yes, clinical stage 3 (pulmonary TB) and CD4 count <350 cells/mm³

2) Does current injecting drug use disqualify the patient for ART?

- ◆ No, active drug use is not a reason to deny care or ART.
- ◆ However, the patient should be referred for counselling and drug treatment, where available.
- ◆ Drug use can be associated with decreased adherence: active IDUs should be carefully counselled and monitored for adherence.

Case study 2 (cont.)

3) When would you start ARV on this patient?

- ◆ After 8 weeks, when the intensive phase of TB treatment is completed

4) What ARV regimen would you use?

- ◆ If the patient continues on rifampicin:
 - EFV-based regimens preferred
- ◆ If the patient continues on HE:
 - EFV or NVP regimens can be given
- ◆ NOTE: The patient has high risk for hepatic toxicity due to chronic HBV and HCV infection, baseline elevated ALT, and use of TB drugs. Check ALT at eight weeks before starting ART and follow closely.

Case study 3

A 20-year-old male patient returns to the clinic for routine follow up. He started ART with d4T/3TC/NVP six weeks ago. Baseline CD4 count was 105 cells/mm³. At four weeks he was feeling well without symptoms and results of routine blood testing (CBC, ALT, AST) were normal. Today he complains of fever, cough with white sputum, and a 1 kg weight loss over the past 10 days.

He started injecting when he was 14 years old and was admitted to a rehabilitation centre four years ago. He was released from the centre six months ago and now lives with his family. He does not currently use drugs.

Case study 3 (cont.)

Physical exam:

Temp 38.0, RR 16, HR 88, BP 120/76

HEENT: no thrush

Neck: no lymphadenopathy

Lungs: rales and wheezing on the upper left side

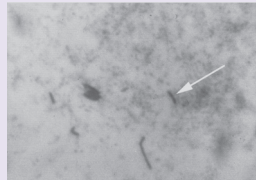
Heart: regular rhythm without murmurs

Abdomen: normal

Skin: no rashes

Case study 3 (cont.)

Sputum AFB:
positive 2+



Source: D Colby

Case study 3 (cont.)**1) What is the diagnosis?**

- ◆ Active pulmonary TB

2) Is this failure of the ART regimen?

- ◆ No, development of active pulmonary TB while on ART does not indicate treatment failure and is common in the first six months of treatment

Case study 3 (cont.)**3) The patient is started on RHZE for TB. Will you stop the ART?**

- ◆ NO! DO NOT STOP THE ART! You should continue ART while treating the TB.

4) Will you change the ART regimen?

- ◆ Concerns about NVP use with rifampicin
- ◆ Preferred regimen is 2 NRTI + EFV, if available
- ◆ Other options: 3 NRTI or continue 2 NRTI + NVP
- ◆ If NVP continued: monitor closely for hepatic toxicity

Treatment and Care for HIV-Positive Injecting Drug Users

The "Treatment and Care for HIV-Positive Injecting Drug Users" training curriculum is designed for clinicians who provide treatment and care, including ART, for HIV-positive injecting drug users. The training curriculum consists of a trainer manual, 12 participant manuals, and a CD-ROM with PowerPoint presentations and reference articles. Topics covered in the curriculum include:

- Module 1: Drug use and HIV in Asia
- Module 2: Comprehensive services for injecting drug users
- Module 3: Initial patient assessment
- Module 4: Managing opioid dependence
- Module 5: Managing non-opioid drug dependence
- Module 6: Managing ART in injecting drug users
- Module 7: Adherence counselling for injecting drug users
- Module 8: Drug interactions
- Module 9: Management of coinfections in HIV-positive injecting drug users
- Module 10: Managing pain in HIV-infected injecting drug users
- Module 11: Psychiatric illness, psychosocial care and sexual health
- Module 12: Continuing medical education
- Trainer manual

The ASEAN Secretariat

70A, Jl. Sisingamangaraja
Jakarta 12110
Indonesia
Phone: +62 21 724 3372, 726 2991
E-mail: public@aseansec.org

World Health Organization

Regional Office for South-East Asia
Mahatma Gandhi Marg
Indraprastha Estate, New Delhi - 110002
India
Phone: +91 11 233 70804
E-mail: hiv@searo.who.int
www.searo.who.int

Family Health International

Asia/Pacific Regional Office
19th Floor, Tower 3, Sindhorn Building
130-132 Wireless Road, Lumpini, Phatumwan
Bangkok 10330, Thailand
Phone: +662 263 2300
E-mail: sunee@fhibkk.org
www.fhi.org

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