treating hiv & aids: a training toolkit

anti-hiv therapy

http://www.aidsmap.com/hatip
Topics covered

- Introduction to anti-HIV therapy (I-II).
- Basics of Antiretroviral Therapy.
- Side-effects of Antiretroviral Treatment.
- Resistance.
- Adherence.
- side-effects.
What is antiretroviral therapy? (1)

- ART combines at least three drugs which stop HIV making copies of itself
- These drugs are called antiretrovirals, or ARVs, because HIV is a retrovirus
- The drugs interfere with HIV’s life cycle in two different ways at once
- It is difficult for the virus to make new copies when attacked in two places at once
What is antiretroviral therapy? (2)

- ART is not a cure
- If treatment is stopped, the virus will come back
- Treatment:
  - Controls HIV
  - Allows the body to recover its ability to fight infections
  - Reduces the chance that a mother will pass HIV to her baby during pregnancy, birth or breastfeeding

http://www.aidsmap.com/hatip
Rules for success

- Take all doses as prescribed – do not miss doses
- Take at least three drugs
- Avoid the use of medications that could reduce the level of ARVs in the blood
- Choose drugs with few serious side effects
- ART has resulted in vast reduction of deaths due to AIDS in Europe and North America since 1996.
- Now beginning to have same effect in Africa and Asia, where affordable.
Reasons treatment may fail (1)

Treatment fails if:

- The drugs are not strong enough to control the virus (most likely in very sick patients) or the patient has many other infections
- The drugs are not taken every day as prescribed (poor adherence)
- Other medicines stop the ARVs from working
- The patient cannot tolerate the ARVs due to side effects
Too sick

■ The patient may have several serious infections which are not treatable

Poor adherence

■ If the drugs are not taken every day, drug levels fall and HIV becomes resistant

■ Missing more than three doses a month increases the risk that treatment will fail

■ Encouraging good adherence is vital

■ Everyone has a part to play in good adherence, not just the patient – doctor, nurse, other clinic staff, community health workers, family, friends
Other medicines may stop ART from working

■ By reducing levels of ARVs in the blood eg TB drug rifampicin

■ Therefore:
  if TB is the most serious AIDS-related infection, treat TB first

■ Important:
  patients must be told that herbal medicines could reduce drug levels

■ Important:
  traditional healers must be told that their medicines could reduce ART drug levels
The patient cannot tolerate the available drugs

- Liver damage and nerve damage, anaemia are possible serious side effects
- Diarrhoea, nausea and vomiting caused by the drugs may sometimes be too much to bear
- Treatment may have to be stopped if these side effects become serious and replacement drugs are not available
Exercise

What are the key reasons for the success or failure of ARV treatment?
How long will treatment keep people alive?

- We don’t know

- ART is still very new in Africa and Asia

- BUT
  - Where enough drugs are available to take several combinations, people are still doing well after 7 – 8 years with good adherence to treatment
  - We are all working together in a great effort to make the best of limited resources
  - Everyone has a part to play
World Health Organisation recommends

- Everyone with AIDS
- Everyone with symptoms of immune system damage (with CD4 count below 350)
- Children with AIDS, or with symptoms and CD4 % below 20
The basics of anti-HIV therapy

- Usually combines at least three drugs, either
  - Three drugs which target different HIV enzymes (eg 2NRTI + PI).
  - Three drugs which target the same HIV enzyme (eg 2NRTI + NNRTI, or 3NRTI)

- There are three main types of antiretroviral drugs:
  - Nucleoside and nucleotide analogue reverse transcriptase inhibitors (NRTIs) which target an HIV protein called reverse transcriptase.
  - Non-nucleoside reverse transcriptase inhibitors (NNRTIs) which also target reverse transcriptase.
  - Protease inhibitors (PIs) which target an HIV protein called protease.
Reverse transcriptase inhibitors

Each class targets HIV’s reverse transcriptase enzyme.

Nucleoside analogue reverse transcriptase inhibitors (NTRIs)
- AZT (zidovudine, Retrovir)
- ddI (didanosine, Videx)
- ddC (zalcitabine, Hivid)
- 3TC (lamivudine, Epivir)
- d4T (stavudine, Zerit)
- abacavir (Ziagen)
- FTC (emtricitabine, Emtriva)

Non nucleoside reverse transcriptase inhibitors (NNRTIs)
- nevirapine (Viramune)
- efavirenz (Stocrin)

Nucleotide analogues (NtRTIs)
- tenofovir (Viread)
Co-formulated reverse transcriptase inhibitors

- **AZT/3TC**
  (Combivir, Generic Brands: Duovir, Virocomb, Zidolam)

- **D4T/3TC**
  (Lamivir-S, Viro LIS, Lamistar)

- **Abacavir/AZT/3TC**
  (Trizivir or Trisivir, Generic Brands: Virol LZ)

- **Nevirapine/d4T/3TC**
  (Generic Brands: Triomune, Viro LNS, Nevilast)

- **Nevirapine/AZT/3TC**
  (Generic brand: Duovir-N)

- **Efavirenz/ddI/3TC**
  (Generic brand: Odivir Kit)
Pronase inhibitors (PIs)

- indinavir (Crixivan)
- ritonavir (Norvir)
- nelfinavir (Viracept)
- saquinavir
  - Invirase – hard gel,
  - Fortovase – soft gel
- lopinavir/ritonavir (Kaletra)
- atazanavir (Reyataz)
Use at least three drugs

It is best to use drugs of two different types
  eg 2 NRTIs and one NNRTI, or two NRTIs and one protease inhibitor

Never use AZT and d4T together

A small amount of ritonavir can increase levels of all PIs apart from nelfinavir

The fewer pills the better

Best to choose a combination in which all pills can be taken at the same time, without regard for food

When choosing a combination, pregnancy and TB need to be considered
EITHER

- Two nucleoside analogues
  - EITHER
    - AZT/3TC (preferred option)
    - d4T/3TC
    - ddl/3TC

PLUS

- A non-nucleoside (NNRTI)
  - EITHER
    - efavirenz
      can be used with rifampicin, cannot be used in pregnancy
    - nevirapine
      cannot be used with rifampicin,

OR

- AZT/3TC/abacavir
  (can be used in pregnancy, can be used with rifampicin, but slightly less potent than AZT/3TC/efavirenz)
Recommended first-line treatment (2)

- **d4T/ddI**
  higher risk of side effects, best avoided

- **Tenofovir**
  where available, best combined with 3TC and efavirenz, less known about other use
Protease inhibitors in resource-limited settings

Possible choices:

- Nelfinavir
  least potent?
- Kaletra (Lopinavir/ritonavir)
  most potent?
- Indinavir/ritonavir
  high number of pills
- Saquinavir/ritonavir
  can be used with rifampicin
- Atazanavir
  once daily, small number of pills, expensive and no generic version yet available

Best reserved for second-line use

- Ritonavir and Kaletra need long term refrigerated storage

- All very expensive compared to first-line therapy

http://www.aidsmap.com/hatip
Exercise: combining drugs

1. Which of the possible cornerstones should not be used with the backbones? Can you say why?

2. Which of the cornerstones should not be used in pregnancy?

3. Which of the cornerstones is best used in patients receiving TB treatment that contains rifampicin?

4. Which of the backbones may have a higher risk of side effects?

5. Which combination is recommended for local use?
Resistance

- Develops when HIV mutants emerge which can reproduce in the presence of a drug.
- Important reason why HIV drugs stop working.
- More missed doses means resistance is more likely.
- Continuing on failing drugs encourages resistance.
- Drug interactions and poor absorption can also contribute to resistance.
- Cross-resistance: some drugs share resistance mutations.
- Tests available to measure drug resistance.
Reducing the risk of resistance

- Keep viral load under control by excellent adherence to treatment - take the treatment as prescribed.
- The lower that viral load falls after starting treatment, the longer it will be controlled.
- Adding one drug to a failing combination is unlikely to keep HIV under control – it wastes the new drug.
- Rising viral load, or failing health, signals need for new combination.
- If the patient experiences problems, they must know who to go to for advice.
The effect of missed doses

Key to symbols
- normal dose
- missed dose
- drug level in system
- level below which virus can replicate
- drug-resistant virus
- drug-sensitive virus

Before treatment begins, viral populations are a mix of mostly drug-sensitive virus, plus a range of drug-resistant viruses.

1. These peaks and troughs show how drug levels in the body rise and fall as doses are taken. Whilst all the doses are taken, the drug's anti-HIV effect is minimised and HIV replication is minimised.

2. Missed doses allow drug levels to fall. HIV replication speeds up again and viral load rises as both drug-sensitive and drug-resistant HIV grows.

3. With the next dose taken, the drug's anti-HIV effect is restored. Drug-resistant HIV may have gained a foothold, however, and will continue to cause a rise in viral load.
Wider use of ARVs may lead to transmission of drug-resistant virus.

People newly infected with HIV in Europe and America may have drug-resistant strains.

Whether someone HIV-positive can become infected with a second drug-resistant strain is less clear.
True or false? Why?

1. HIV cannot make errors when it copies itself.

2. Resistance means that a drug does not work against HIV.

3. There is less risk of resistance if a person takes all three drugs in a combination.

4. The chance of developing resistance increases if people do not take medication as prescribed.

5. A virus which is resistant to a drug cannot be passed onto another person.

6. Resistance is only a problem for nevirapine and 3TC.
Our own experience of taking medicines

1. Describe your own experience of taking medicines to your partner.

2. How easy was it to find information about the medicines?

3. How easy was it to follow the instructions on how to take the medicines?

4. What made it easy or hard to take the medicines?

■ Please respect requests for confidentiality.
Practice taking ARVs

see handout
Adherence: issues for those on therapy (1)

- People must understand that treatment is a long-term commitment. It cannot be stopped and started.

- People must understand that treatment must not be stopped if they start to feel better.

- Mental health
  People who are depressed, isolated may have difficulties.

- Health beliefs
  If people believe drugs are doing harm, they are more likely to miss them.

- A suitable regimen
  If the drugs are inconvenient to take, they will not be taken.

- Information
  If the patient does not understand when, why, how, the drugs will not be taken properly.

- Side-effects
  The patient may stop taking the drugs if the side effects cannot be controlled.
Practice first.

Learning from the experience of others will help patients take medication.

So will support from family, friends. Disclosure to another person who will help in taking treatment is important.

Develop a routine – take pills at the same times each day.

Seek help quickly if problems occur in taking pills.
Don’t make assumptions about patient adherence – ask questions and discuss solutions.

BEFORE TREATMENT:

- Do you know that the medicines must be taken for the rest of your life? Your life depends on taking them every day at the right times.
- If you stop, you will become ill (not immediately, but after months or years).
- Do you know that you should not share these medicines with family or friends?
- Have you told anyone that you are HIV-positive? Telling someone else who can help you take your medicines every day will help you.
- Check the patient’s clinic attendance – ask about reasons for missed appointments.
- How far do you have to travel to the clinic, and do you think you can keep regular appointments here?
**Adherence: issues for health care workers**

- Don’t make assumptions about patient adherence – ask questions and discuss solutions.

**AFTER TREATMENT STARTS:**

- Ask questions in a respectful and non-judgmental way. Ask in a way that makes it easier for patients to be truthful.
  - “Many patients have trouble taking their medications. What trouble are you having?”
  - “Can you tell me when and how you take each pill?”
  - “When is it most difficult for you to take the pills?”
  - “It is sometimes difficult to take the pills every day and on time. How many have you missed in the last 4 days (insert agreed time period)?”

- Ask about stigma related to taking the pills.
- Count pills.
- How many pills forgotten yesterday, last 3 days, last month?

http://www.aidsmap.com/hatip
Possible reasons for poor adherence

■ Most common reason: ‘I forgot’
  ■ Always try to discover the reason for forgetting
  ■ If several doses missed, is there a pattern

■ Other possible reasons:
  ■ Difficulties in taking pills around others
  ■ Misunderstanding about how to take pills (revise)
  ■ Scheduling problems – work, travel, family events
  ■ Ran out of pills
  ■ Depressed
  ■ Excess alcohol use
Discussion

- How do we respond to each of the common reasons for missing doses?
- How can we help patients with future pill taking?
Understanding why side-effects occur

- All drugs have unwanted side effects – most are very minor
- Often difficult to predict who will experience side effects, and how much of a problem they will be for an individual
- Two types
  - Allergic
    - eg rash (nevirapine), hypersensitivity (abacavir)
  - Direct effect of drug
    - eg nerve damage (stavudine), anaemia (AZT)
Types of side-effects

Initial short-term side-effects:

- Most occur in the first months of treatment
- Consider treatment with anti-nausea, anti-diarrhoea, headache medication: be prepared.
- Suspected allergic reaction to nevirapine or abacavir? Alert treatment centre.
- Dose escalation of nevirapine – dose will increase after 14 days if no severe rash or liver toxicity
- Side effects are common cause of missed doses.

Longer-term side-effects of ART not well understood:

- Lipodystrophy.
- Metabolic abnormalities.
- Lactic acidosis and mitochondrial toxicity.
Common side-effects (1)

**Anaemia** – loss of red blood cells - most common with AZT
- Monitor haemoglobin regularly
- Fatigue most common early sign, out of breath
- Reduce AZT dose for short period – if no improvement, or relapse upon restoration of full dose, switch from AZT
- Reserve blood transfusion for most serious cases due to risk of complications

**Diarrhoea** – more common with protease inhibitors, also ddI
- If PIs used, loperamide may relieve diarrhoea
- Rehydrate.
- Rice water – use other local remedies too
- More fibre in food – this goes against normal diarrhoea advice, but may work with nelfinavir diarrhoea
- If severe and long-lasting, investigate other causes.

**Nausea** – common with NRTIs and PIs in first months
- Taking AZT with food may reduce nausea
- Anti-nausea drugs if severe
- Ginger tea or chewing ginger root may help
Common side-effects (2)

Fatigue – may occur in first few weeks as body gets used to drug
- If it does not improve, it may be sign of anaemia caused by AZT treatment
- If appears later with stomach pain, nausea, weight loss – see doctor – may be sign of lactic acidosis or liver toxicity

Liver toxicity/hepatitis – weight loss, loss of appetite, nausea and vomiting, fever, abdominal pain, itchy skin, and an enlarged or tender liver. Jaundice
- If nevirapine-related, switch to efavirenz or delay dose escalation according to local guidelines
Common side-effects (3)

Vivid dreams, dizziness, unable to sleep, reduced tolerance of alcohol – efavirenz

- Usually starts within days of taking first dose, most patients report improvement after 6-8 weeks
- More serious mental health problems can occur in people with previous history – either change to nevirapine or provide antidepressants

Nerve damage (peripheral neuropathy) - d4T, ddI, isoniazid

- Tingling, burning, shooting pain in the feet, legs
- Stop until pain goes, then resume d4T at lower dose
- Painkillers have limited effect; avoidance of severe damage is preferable – warn patients of need to report symptoms early
- Isoniazid should be taken with vitamin B6 to reduce risk of nerve damage
Common side-effects (4)

Rash – nevirapine

- Occurs in first month on treatment, often after NVP dose increased at day 14, more likely in women
- Very serious rash – 1 to 5 in 1000 patients – peeling skin – must stop nevirapine – life threatening reaction
- Serious rash – much of body – 7 in 100 patients – seek medical advice
- Mild rash – 1 in 10 – avoid scratching, overheating, irritant chemicals in soap etc, synthetic fibres

Rash – efavirenz

- between 3 and 5 in 100 patients experience mild to moderate rash

Rash – abacavir

- often preceded by fever, aches and pains, nausea, breathlessness – hypersensitivity reaction – stop immediately
Common side-effects (5)

Neutropenia - loss of neutrophils, white blood cells that fight bacterial infections

- Caused by AZT, d4T, drugs used to treat cancers, ganciclovir
- Laboratory monitoring: neutrophil count
- Clinical monitoring: recurrent bacterial infections in mouth, nose, throat, chest; if fever = seek medical help immediately. This is an avoidable side effect.
- Symptoms:
  - Fever, aches, pains, chills and sweating
  - Sores in the mouth or gums
  - Chest infections – cough producing lots of green mucus
  - Very sore throat and fever
  - Ear ache and fever
  - Discharge from the genitals
  - Sudden swelling around cuts or sores on the skin

- Reduce dose or change to another drug
Common side-effects

Thrombocytopenia - low platelet count

- Rare but potentially serious side effect of AZT
- Platelet count below 10 million/ml
- Clinical symptoms
  - Nose bleeds
  - Frequent bruising
  - Small pinpoint red spots
  - Blood in the stools or urine
  - More severe: coughing up blood

- Switch from AZT where it is likely to be the cause

http://www.aidsmap.com/hatip
**Lactic acidosis** – caused by build up of lactate, produced when cells burn energy

- Most likely with d4T treatment, pregnant women, high body weight, women may have higher risk
- Symptoms: nausea (feeling sick), vomiting, bloating, abdominal pain and lack of appetite, as well as malaise, and difficulty in breathing, liver pain
- Stop nucleoside analogue treatment, do not resume d4T, support breathing, treat with bicarbonate
Group exercise: side-effects

1. Identify the main ARVs used in the locality
2. Divide into groups of four
3. List the main side effects of ARVs used in the locality
4. Divide side effects into two groups
   a. Serious and life threatening
   b. Side effects which can be relieved
5. Brainstorm local remedies that might relieve less serious side effects
6. Feed back to the main group
Key side-effects by drug or drug class

See handout
# Symptoms of Lipodystrophy

<table>
<thead>
<tr>
<th>Fat gain (lipohypertrophy)</th>
<th>Fat loss (lipoatrophy)</th>
<th>Metabolic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased waist size</td>
<td>facial wasting, especially of the cheeks</td>
<td>changes in blood fat (lipid) levels</td>
</tr>
<tr>
<td>Increased breast size</td>
<td>loss of subcutaneous fat in all parts of the body, most visibly in the limbs</td>
<td>blood sugar increases</td>
</tr>
<tr>
<td>‘buffalo hump’ (fat accumulation around the neck and upper back)</td>
<td>wasting of the buttocks</td>
<td>insulin resistance</td>
</tr>
<tr>
<td>fat accumulation around the neck and jaw (‘moon face’)</td>
<td>prominent leg veins</td>
<td></td>
</tr>
<tr>
<td>fat deposits in other locations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

http://www.aidsmap.com/hatip
What causes lipodystrophy?

A number of factors have been associated with body fat changes

Not just caused by protease inhibitors

- treatment with protease inhibitors and nucleoside analogues together
- specific drugs
- type and duration of anti-HIV therapy
- duration of HIV infection or low CD4 count

Fat accumulation and fat loss may have separate causes

- gender
- age
- race
- higher body mass and fat prior to treatment

http://www.aidsmap.com/hatip
HAART and the heart

- Some HIV drugs, especially PIs, can increase fats and sugar levels which may increase heart disease risk.
- Several large studies have found no relationship between increased fats and sugars and heart disease risk.
- The DAD study found the longer you are on HAART, the higher the risk of heart disease.
- Still fairly low risk, and benefits of HAART outweigh risks, in short term.
- Stop smoking, eat healthily, and exercise more.