Learning outcomes

• To consider the impact of highly active anti-retroviral therapy (HAART) in the management of HIV infection
• To understand HAART is only available for a lucky minority
• To discuss the care management issues for people living with HIV infection
Living with HIV: a chronic illness

• Diagnosis of HIV does not present the infected person with an established or predictable prognosis.
• It introduces the individual to the prospect of increasing ill health in the context of a changed lifestyle, and the very real threat of death after some unknown period.
• Uncertainty of HIV - May have a fluctuating course involving periods of good health followed by periods of illness
HIV infection

• **Asymptomatic**
  • May be asymptomatic for 1-10+ years
  • How long will you remain asymptomatic? Patients tend to be diagnosed at a relatively late stage in the UK over 30% present with a CD4 count of less than 200.

• **Symptomatic**
  • Symptoms may be caused/ exacerbated by HIV infection or by antiretroviral therapy
  • There may be a need to weigh the benefit of starting treatment early against the risk of deferring therapy.
  • May have periods of ill health / hospitalization that could have effects on relationships/family/work.
Early stage HIV infection

Early infection:
• patient presents with severe flu-like illness while seroconversion takes place

• HIV diagnosis made by
  • PCR test (detects HIV RNA)
  • ELISA / Western Blot (detects antibody)

• Post-exposure prophylaxis (PEP)
  • following early infection, early HAART can suppress the virus to levels where it cannot take-hold in the lymph nodes
Mid stage HIV infection

Middle infection (1-5) years

• CD4 cell levels remain >500 cells / ml

• initiation of ART will be determined by CD4 and viral load levels and physician experience

• some transient infections may occur

• the ability of the patient to suppress viral blood levels is a prognostic factor for time without AIDS
End stage HIV infection

Late infection (AIDS):
   Viral load high >50,000 copies/ml
   CD 4 cells <100 cells/ml

A CD4 count below 200/ml will give a person with HIV an AIDS diagnosis, irrespective of the presence of major opportunistic infections. Of course, with such a reduction in CD4 count, the patient is vulnerable to opportunistic infection.
HAART – HIV’s Treatment Revolution

Highly active anti-retroviral therapy
• Offers new hope
• Delays onset of symptoms
• Delays diagnosis of AIDS
• Extends and improves quality of life
Effective therapy for HIV

• HIV is now a treatable disease

• In 1995 there was the advent of HAART, with three anti-viral agents used in combination
• Mortality has progressively declined as anti-viral therapy has become progressively more aggressive, moving from mono to dual to triple therapy.
Therapy

- ART (Anti-Retroviral Therapy)
- HAART (Highly Active Anti-Retroviral Therapy)
- Combo/combination therapy (drugs are always given in combination, at least three drugs)
Key factors to consider when selecting first-line therapy

- Adherence
- Potency
- Durability
- Side effects
- Sanctuary site penetration
- Resistance profile
- Metabolic/intracellular interactions
HIV infects a CD4 cell.
HOW HAART Works

1. **Nucleus**
   - RNA is reverse transcribed into DNA by reverse transcriptase.

2. **Reverse transcriptase**
   - RNA is transcribed into DNA by reverse transcriptase.
   - DNA is then released from the virus into the host cell.

3. **Protease**
   - Protease inhibitors are used to stop the degradation of the virus.

4. **RNA**
   - RNA is released from the virus into the host cell.

**Fusion inhibitors**
- Work outside the cell to prevent the first stage of HIV replication.
- Prevent HIV from entering the CD4 cell by blocking fusion of the outer membrane of the virus with the cell membrane.

**Non-nucleoside reverse transcriptase inhibitors**
- Bind to reverse transcriptase and inhibit the enzyme.
- Stop HIV replication by preventing the conversion of RNA to DNA.
- These drugs are called "nonnucleoside" inhibitors because even though they work at the same stage as nucleoside analogues, they act in a completely different way.

**Nucleoside/Nucleotide analogues**
- The first effective class of antiretroviral drugs was the nucleoside analogues.
- They act as false substrates for reverse transcriptase, causing chain termination.
- The resulting DNA is incomplete and this prevents HIV replication.
- Nucleotides work in a similar way to nucleosides but they have a different chemical structure.

**Protease inhibitors**
- Work at the last stage of the viral replication cycle.
- Prevent HIV from being successfully assembled and released from the infected CD4 cell.
Groups of drugs

- **NRTIs**: nucleoside reverse transcriptase inhibitors
- **NNRTIs**: non-nucleoside reverse transcriptase inhibitors
- **(NtRTIs)**: nucleotide reverse transcriptase inhibitors
- **PIs**: protease inhibitors
- **Integrase inhibitors**
- **Fusion inhibitors**
Current BHIVA guidelines on Treatment of HIV

When do you start treatment?

• When patient agrees the time is right
• When benefits > risks
• If there is a major opportunistic infection
• CD4 drops < 350 cells/ml
• Consider if CD4 350 -500 viral load >30, 000 copies/ml
Is 500 the new 350?

• Previously treatment at higher CD4 counts were avoided because of the problems associated with treatment failure due to poor compliance, thus resulting in the emergence of resistant virus.
• However, recent evidence from the US suggests a 70% improvement in survival for patients who initiate treatment with a CD4 count between 351 and 500
Choosing a HAART regime

Figure 1. Considerations for choice of initial regimen.

- Underlying Conditions: Pregnancy, Hepatitis, CV disease
- Drug-Drug Interactions
- Lifestyle: Dosing, Pill burden
- Toxicity: Short term, Long term

Used with permission. William O’Brien, MD, MS, University of Texas Medical Branch at Galveston, Galveston, Texas.
Aims of therapy

• Suppression of the virus
• Elevation of CD4 count
• Improved quality and length of life
• Slowing disease progression
• Preventing opportunistic infections (OIs)
Challenges of HAART - 1

• Pill burden
• Punctuality
• Side-effects
• Dietary restrictions
• Confidentiality
• Other medication
Challenges of HAART - 2

• Social life
• Ongoing therapy
• Drug interactions (legal and illegal ones)
• Risk of resistance
Factors encouraging adherence to therapy

- Easily incorporated into patient lifestyle
- Convenient and simple dosing
- Dosing not affected by food
- Good tolerability
- Manageable side-effect profile
- Maintained quality of life
- Compact, easy-to-swallow tablets
Side effects – short term

- Nausea, vomiting, diarrhoea
- Allergic reactions
- Cognitive changes (insomnia, depression)
- Hepatitis or pancreatitis
- Fatigue
- Etc.

None of them has to occur, and most of them will stop after a while
Side effects – long term

• Peripheral neuropathy (painful arms and legs)
• Liver damage
• Lipodystrophy (abnormal fat distribution – losing in some areas, gaining at others)
• ? Diabetes (raised blood glucose levels)
• ? Cardiac disease (raised cholesterol)
• Etc.
Resistance is often a problem
HIV replication and mutation

- Rapid replication: as many as 10 billion copies of the virus a day are formed in HIV infection.
- HIV’s reverse transcriptase moderated replication is “sloppy”. There is no “proof-reading” function.
- Therefore, an average of one mutation to three HIV genomes copied.
The virus mutates - treatment fails

**Virus population** - replication & mutation

**Drug reduces replication** - but does not eliminate it

**Mutation via selection by drug** - leads to virus with reduced drug sensitivity

**Replication increases over that pertaining immediately post start of therapy** – this leads to more mutation & selection

Rate at which evolution takes place depends on viral genetics, growth dynamics, drug properties (pharmacokinetics & pharmacodynamics), & patient adherence.
Treatment Strategies

• Monotherapy
• Dual therapy
• Triple therapy (Current Standard of Care)
• Quad therapy etc
• Induction/maintenance
• Intensification
• Pulse therapy/ drug holidays
• Cycling
• Sequencing
• Salvage
Optimum HAART regimes

• The aim of HAART is to achieve a viral load of <50/ml within 4-6 months of starting therapy
• Efavirenz (an NNRTI) should be considered first line Rx for all patients commencing therapy
• Boosted PIs (PIs with the addition of low-dose Ritonavir) are useful for those patients who have built up to resistance to reverse transcriptase inhibitors
Current BHIVA guidelines on switching treatment

When to switch?

- increase in viral load > 50 copies/ml at 24 weeks (2 tests, at least 2 weeks apart)
- unacceptable toxicity
- poor adherence
- resistance testing recommended
- if toxicity arises, single agent switch with a similarly potent drug, but with better toxicity profile
Resistance

- Poor adherence
- Poor absorption
- Pre-therapeutic resistance (10%)
- Doses are inadequate (miscalculation or patient shares medication)
- Mutation
- Cross-resistance
Adherence Issues

- **Adherence is a process not a single event**
- Any HAART regime should be individualized in order to achieve the best potency, adherence & tolerability; to minimize potential toxicity; & to avoid any likely drug - drug interactions.
- A measurement of a regimen’s success is achieving a viral load of less than 50 HIV 1 copies/ml within 6 - 9 months.
- Interventions to support adherence should be multifaceted, responsive to the needs of the individual & an integral part of ongoing care (Haynes et al, 1996)
Main reasons for discontinuing HAART

- Toxicity: 58.3%
- Virologic failure: 14.1%
- Nonadherence: 19.6%
- Other: 8.0%

N = 312 discontinuations

Source: AIDS Read © 2003 Cliggott Publishing, Division of SCP Communications
95% adherence is required to achieve undetectable viral loads in 80% of patients.
Adherence in chronic illnesses

• Adherence levels are low in chronic disease such as diabetes, asthma and hypertension only 50% patients remain adherent over time
• Frequency of dosing is critical
• Once a day and twice a day regimens are associated with significantly better adherence (73% and 70% respectively) than three times daily (52%) and four times daily (42%) regimens
• Adherence changes over time
Promoting Adherence

• Help ensure through advice and information, that the patient commits to therapy and wants to adhere.
• Help patients fit medication regimes into daily life, instead of structuring life around medication.
• Providing memory aids to establish & maintain a pill taking routine.
• Treat any underlying mental health problems.
• Management of side effects.
• Understanding the potential risks & benefits of therapy in the short & long term.
• Make it easy to access advice and information, e.g. Helpline numbers.
Even with total adherence, problems remain ….
Role of the HIV Nurse

- Principle Aims of HIV Nurse
  - To provide seamless holistic care
  - Adherence education and support through treatment changes and adverse events
  - Information provision and advice around care decisions
  - Structured ongoing follow up
  - To act as facilitators for access to other services
Typical support offered by HIV specialist Nurse

• Seeing the patient prior to starting therapy
• Two weeks into therapy (which will coincide with Nevirapine dose escalation) where they will take baseline bloods
• Four weeks into therapy where they will take a repeat viral load and monitor bloods
• Eight weeks into therapy to monitor post-short term transient side effects
• An offer of ongoing support at six monthly intervals
Summary

• Treatment success with antiretroviral therapy is directly related to adherence with prescribed medication
• Decreasing the complexity of regimens encourages adherence and may help sustain long term efficacy
• Patients need regular help and support to maintain good adherence
• Medication should be tailored to fit into patients lifestyle to help with adherence
Time Out Exercise

• In small groups, please discuss what factors are important for the nurse to consider with regard to adherence, when counselling a patient considering commencing HAART.
References 1

• Chippindale, S French, L. (2001) HIV counselling and the psychosocial management of patients with HIV or AIDS BMJ (322):1533-1535
References 2


• [www.aidsmap.com](http://www.aidsmap.com)

• [www.i-Base.org.uk](http://www.i-Base.org.uk)