About the virus and its epidemiology

Why does HIV matter?

Infected T-helper cells
T-helper cells …… help!
Regulatory cells that co-ordinate the immune system
Immune system protects from infection, malignancies, foreign bodies…
Critical levels ~350 and 200 cells µL

What is it?

Human immunodeficiency virus
Not the same as AIDS - acquired immunodeficiency syndrome
AIDS is end-stage of HIV infection
Discovery – controversial LAV/HTLV III
Tropism for cells carrying CD4 molecule – especially T-helper cells

History

Science and politics
Number 1 problem for people with HIV in the UK

First case series

Cluster of Cases of the Acquired Immune Deficiency Syndrome linked by sexual contact

Cluster of Cases of the Acquired Immune Deficiency Syndrome linked by sexual contact

4 H's

1982, CDC added another risk factor – being of Haitian origin

Led to ‘4 H’s’
1. Homosexual
2. Heroin addict
3. Haemophiliac
4. Haitian origin
More information emerges

Epidemiologic Notes and Reports Pneumocystis carinii Pneumonia among Persons with Hemophilia A

December 10, 1982 / 31(48):652-4

Epidemiologic Notes and Reports Possible Transmission-Associated Acquired Immune Deficiency Syndrome (AIDS) — California

December 17, 1982 / 31(49):665-667

Unexplained Immunodeficiency and Opportunistic Infections in Infants — New York, New Jersey, California

and more....

An HIV-1 Transmission Case Possibly Associated with Microsexual Abuse

Fraser (2004) PNAS 101 6146-6151

Infectious but obvious
Infectious and not obvious

Not very infectious and obvious
Not very infectious and not obvious

Control depends on $R_0$ and asymptomatic period

HIV Transmission Through Breastfeeding: Still Possible in Developed Countries

MMWR Morbidity and Mortality Weekly Report

HIV in the United Kingdom: 2014
Annual new HIV and AIDS diagnoses and deaths: UK, 1981-2013
**HIV tests**

**HIV diagnosis (Antibody/Antigen)**
Enzyme Immunoassays (EIAs)
Rapid tests
Western blot (WB)

**Early diagnosis in infants**
p24 (Antigen)
PCR (Polymerase Chain Reaction genome)

**Initiation and monitoring of ART**
CD4
Viral Load – note undetectable ≠ none

---

**Diagnostic markers**

![Graph showing HIV RNA, p24 Ag, and Antibodies levels over time](image)

---

**HIV types and origins**

---

**Replication cycle and drug targets**

Initial binding
CD4 molecule
Secondary binding
Fusion
Reverse transcription
Integration
Protein production and processing
Assembly
Budding and maturation

---

**About the immune system**
The immune system

<table>
<thead>
<tr>
<th>Innate (non-specific)</th>
<th>Acquired (specific)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>T lymphocytes</td>
</tr>
<tr>
<td>Macrophages</td>
<td>T helper cells (CD4)</td>
</tr>
<tr>
<td>Natural killer cells</td>
<td>T cytotoxic (CD8)</td>
</tr>
<tr>
<td>Acute phase proteins</td>
<td>B lymphocytes</td>
</tr>
<tr>
<td>Complement</td>
<td></td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>Plasma cells</td>
</tr>
<tr>
<td></td>
<td>Memory cells</td>
</tr>
</tbody>
</table>

Lymphocytes

Four main classes
1. B (plasma cell)
2. T cell
   - Helper (CD4)
   - Cytotoxic (CD8)
3. Natural regulatory (nTreg)
4. Natural killer cells (NK) - innate

T helper cells (CD4+)

- Help B cells produce antibody
- Increase microbiocidal activity of macrophages
- Recruit neutrophils, basophils and eosinophils to site of infection

"Through the production of cytokines orchestrate the full panoply of immune responses"


Cytotoxic T cells (CD8+)

- Detect virally infected cells because they display viral rather than host peptides in association with MHC Class I
- Release of cytotoxins that damage the cell leading to caspase enzyme cascade and apoptosis
- Some bystander damage may occur
- Sometimes referred to as cell-mediated immunity

B cells

- Activation of B cells occurs via antigen recognition by B cell receptors and co-stimulatory, secondary activation signal provided by either helper T cells or the antigen itself
- Stimulates B cell proliferation and the formation of germinal centres
- B cells differentiate into plasma cells or memory B cells
- As all B cells derived from a specific progenitor B cell are clones that recognize the same antigen epitope

Plasma and memory cells

- Found in the spleen and lymph nodes – secrete different classes of clonally unique antibodies that are found in the blood
- A small number of B cells develop into memory B cells
  - Express high-affinity surface immunoglobulins (mainly IgG)
  - Survive for a longer period of time
  - Enable a rapid secondary response
Antibody classes

<table>
<thead>
<tr>
<th>IgA</th>
<th>mucosal, no maternal transfer but found in breast milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgD</td>
<td>bound to B cells</td>
</tr>
<tr>
<td>IgE</td>
<td>general inflammation, macroparasites</td>
</tr>
<tr>
<td>IgG</td>
<td>main serum antibody, maternally transferred</td>
</tr>
<tr>
<td>IgM</td>
<td>produced by naive plasma cells</td>
</tr>
</tbody>
</table>

CD4 (cluster of differentiation)

- Molecule found on the surface of cells of the immune system, including T-helper cells
- Monocytes/macrophages
- Dendritic cells
- Glial cells

- Generically used to mean T-helper cells
- Main receptor for HIV binding

A good immune response requires T-cell help

- Antibody production does not require T-cell help, but a good response does
- Some antigen can stimulate B-cell directly, known as T-independent
- Repeating antigens (e.g., polysaccharides) bind and cross-link B-cell surface antigen
- Mainly IgM; poor affinity; limited memory

Relationship between VL and CD4 count

CD4+ Lymphocytes Count (cell/mm³)

- Primary infection
- Acute HIV:ige immune response: activation of immune cells
- Opportunistic infections: clinical latency
- Advanced HIV infection: death

- HIV RNA copies per ml plasma
HIV - CD4 counts, typical infections and when to treat?

Key issue 1: inverse relationship between HIV VL and CD4 count
Key issue 2: ART to reduce VL (HAART)

Patterns of HIV Disease Progression

Typical Progressors 8-10 years
Rapid Progressors <3 years
Long-term Non-progressors >10-15 yr

Criteria for good antimicrobial

High selective toxicity to the pathogenic microorganisms in host
Have no or less toxicity to the host
Low propensity for resistance
Not induce hypersensitivies in the host
Rapid and extensive tissue distribution
Free of interactions with other drugs
Relatively inexpensive

WHO immunological classification for established HIV infection

<table>
<thead>
<tr>
<th>Immune suppression</th>
<th>&lt;11 months</th>
<th>12-35 months</th>
<th>36-59 months</th>
<th>&gt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>None/non significant</td>
<td>&gt;35%</td>
<td>&gt;30%</td>
<td>&gt;25%</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Mild</td>
<td>25-34%</td>
<td>25-30%</td>
<td>20-25%</td>
<td>350-499</td>
</tr>
<tr>
<td>Advanced</td>
<td>20-24%</td>
<td>20-24%</td>
<td>15-19%</td>
<td>200-349</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;20%</td>
<td>&lt;20%</td>
<td>&lt;15%</td>
<td>&lt;200 or &lt;15%</td>
</tr>
</tbody>
</table>

Absolute number per mm³ or %

Why viruses are tricky to treat – ‘the tree of life’

Phylogenetic Tree of Life

Bacteria
Archaean
Eucaryota

Viruses – obligate intracellular parasites; reproduce inside host cells
Goals of Therapy

- Reduced opportunistic infection & death
- Increased CD4
- Suppressed viral load
- Improved quality of life (health)
- Reduced 'non-HIV-related' illnesses
- Reduced CVD risk / fracture risk / CNS disease risk?
- Prevent infection / reduce onward transmission

A history of antiretroviral therapy

- What should the approach be in the future?
  - Deferral of therapy
  - ‘Hit hard, hit early’
  - ‘Sequential monotherapy’ with PI/NRTIs
  - Sequential/NRTI monotherapy and dual NRTI therapy
  - AZT monotherapy
  - No ARV therapy

Available Antiretrovirals 2015

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>Protease Inhibitors</th>
<th>Integrate Inhibitors</th>
<th>NNRTI Class</th>
<th>Fusion Inhibitors</th>
<th>Drug</th>
<th>NRTI Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir (TDF)</td>
<td>Emtricitabine (FTC)</td>
<td>Atazanavir (ATV)</td>
<td>TDF</td>
<td>9</td>
<td>EFV</td>
<td>3082</td>
<td>100</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Abacavir (ABC)</td>
<td>Lopinavir (LPV)</td>
<td>FTC</td>
<td>9</td>
<td>EFV</td>
<td>3082</td>
<td>100</td>
</tr>
<tr>
<td>NVP</td>
<td>Darunavir (DRV)</td>
<td>Ritonavir (RTV)</td>
<td>TDF</td>
<td>9</td>
<td>EFV</td>
<td>3082</td>
<td>100</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>Rilpivirine (RPV)</td>
<td>MDC866</td>
<td>TDF</td>
<td>9</td>
<td>EFV</td>
<td>3082</td>
<td>100</td>
</tr>
</tbody>
</table>

Group | NHS list price (£) | ~30% discount (£) | ~60% discount (£) | Date |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir (TDF)</td>
<td>2880</td>
<td>2014</td>
<td>403</td>
<td>2017</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>1956</td>
<td>1369</td>
<td>274</td>
<td>Now (3TC)</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>2136</td>
<td>1495</td>
<td>300</td>
<td>2016</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>1608</td>
<td>1126</td>
<td>225</td>
<td>Now</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>2400</td>
<td>1680</td>
<td>336</td>
<td>Now</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>2040</td>
<td>1428</td>
<td>285</td>
<td>Now</td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td>2400</td>
<td>1680</td>
<td>336</td>
<td>Now</td>
</tr>
<tr>
<td>Darunavir (DRV)</td>
<td>3600</td>
<td>2520</td>
<td>504</td>
<td>2017</td>
</tr>
<tr>
<td>Atazanavir (TIZ)</td>
<td>3636</td>
<td>2545</td>
<td>509</td>
<td>2017</td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td>5652</td>
<td>3956</td>
<td>205</td>
<td>2017</td>
</tr>
</tbody>
</table>

Per person per year £ sterling
When to start ART?

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Start</th>
<th>Consider</th>
<th>Defer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHIVA (2012)</td>
<td>Symptomatic CD4 &lt; 350</td>
<td>CD4 350-500 in specific circumstances</td>
<td>CD4 &gt; 500</td>
</tr>
<tr>
<td>European (2013)</td>
<td>Symptomatic CD4 &lt;500</td>
<td>CD4 &gt;350 Co-infection &gt;50yrs</td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CD4 350-500 in specific circumstances</td>
<td>Reduce transmission</td>
</tr>
</tbody>
</table>

When to start ART?

<table>
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<tr>
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<td>CD4 &gt;350 Co-infection &gt;50yrs</td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce transmission</td>
<td>Conditions associated with HIV</td>
</tr>
</tbody>
</table>

When to Start Antiretroviral Therapy

### Case for early treatment
- Immune system recovery more likely
- Possible prevention of non-opportunistic events e.g. death, CVD, non-AIDS cancers
- Risk of clinical disease progression is higher off therapy even at high CD4 counts (SMART)
- Current regimens are more convenient and less toxic, so longer time on ART is now possible
- May reduce HIV transmission

### Case against early treatment
- Eradication not possible
- Toxidilities
- Risk of AIDS is low until the CD4 count is below 200/µL
- Once you start ART, it is risky to stop
- Adherence will be extremely difficult to maintain
- Risk of accumulation of drug resistance, which closes off future options

What to start

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommended</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHIVA (2015)</td>
<td>NRTI - Truvada (TDF/FTC)</td>
<td>NRTIs Kivexa (ABC/3TC)</td>
</tr>
<tr>
<td></td>
<td>Integrase inhibitors</td>
<td>NNRTIs</td>
</tr>
<tr>
<td></td>
<td>Raltegravir</td>
<td>Efavirenz</td>
</tr>
<tr>
<td></td>
<td>Dolutegravir</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elvitegravir/cobi</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Protease inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atazanavir/r</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Darunavir/r</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NNRTI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rilpivirine</td>
<td></td>
</tr>
</tbody>
</table>

Resistance as the Ultimate Consequence of Non-Adherence

**Resistance**

Adherence and the emergence of resistant virus strains

- Intermediate Adherence Leads to Drug-Resistant HIV

About prophylaxis
**Risk of transmission per exposure**

<table>
<thead>
<tr>
<th>Nature of exposure</th>
<th>Estimated risk of transmission per exposure from an HIV+ person not on ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptive anal intercourse</td>
<td>1 in 90</td>
</tr>
<tr>
<td>Receptive anal intercourse with ejaculation</td>
<td>1 in 65</td>
</tr>
<tr>
<td>Receptive anal intercourse without ejaculation</td>
<td>1 in 170</td>
</tr>
<tr>
<td>Insertive anal intercourse</td>
<td>1 in 666</td>
</tr>
<tr>
<td>Insertive anal intercourse not circumcised</td>
<td>1 in 161</td>
</tr>
<tr>
<td>Insertive anal intercourse and circumcised</td>
<td>1 in 909</td>
</tr>
<tr>
<td>Receptive vaginal intercourse</td>
<td>1 in 1000</td>
</tr>
<tr>
<td>Insertive vaginal intercourse</td>
<td>1 in 1.219</td>
</tr>
<tr>
<td>Semen splash to eye</td>
<td>&lt;1 in 10,000</td>
</tr>
<tr>
<td>Insertive oral sex (giving fellatio)</td>
<td>&lt; 1 in 10,000</td>
</tr>
<tr>
<td>Blood transfusion (one unit)</td>
<td>1 in 1</td>
</tr>
<tr>
<td>Needlestick injury</td>
<td>1 in 333</td>
</tr>
<tr>
<td>Sharing injecting equipment (includes chemsex)</td>
<td>1 in 149</td>
</tr>
<tr>
<td>Human bite</td>
<td>&lt; 1 in 10,000</td>
</tr>
</tbody>
</table>

**Antiretroviral therapy used to prevent HIV transmission**

- Pre Exposure Prophylaxis (PreP)
- Post Exposure Prophylaxis (PEP)
- Post Exposure Prophylaxis following sexual exposure (PEPSE)
- Treatment as Prevention (TasP)

**Stages of HIV infection**

- Primary HIV infection
- Asymptomatic HIV infection
- Symptomatic HIV infection
- AIDS diagnosis

**What is PEP?**

The use of a combination of antiretrovirals by HIV-negative individuals for a short period of time after a suspected or known exposure to HIV

- Must be started as soon as possible but within 48-72 hours after the exposure
- Must be taken everyday for 28 days
- Must avoid additional exposures while taking PEP

**PreP Pre-Exposure Prophylaxis**

To prevent HIV in those who are at high risk of exposure to HIV

By taking one pill (Truvada) once a day

PrEP is only for people who are at ongoing substantial risk of HIV infection

Single high-risk events of potential HIV exposure PEP should be used

**Who is at high risk?**

- Injecting drug users
- Anyone who is in an ongoing relationship with an HIV-positive partner
- Those who have unprotected sex with partner without a known HIV status who may be at high risk for HIV
- Discordant couples wanting a baby
The BHIVA/BASHH Position Statement on pre-exposure prophylaxis

We recommend that ad hoc prescribing is avoided…that PrEP is only prescribed in the context of a clinical research study in the UK

Health-care workers should note that PrEP is one of several prevention tools…condoms and treatment of positive partners are too compelling to be ignored

While further evidence is gathered, validated behavioural interventions, regular HIV testing, the diagnosis and treatment of other sexually transmitted infections, and intensive health-promotion activities according to current BASHH-BHIVA guidelines should be implemented in preference to PrEP

Summary recommendations

- PEPSE should be initiated as soon as possible after exposure, preferably within 24 hours, but can be considered up to 72 hours
- Do not recommend giving PEPSE beyond 72 hours
- Duration of PEPSE should be 28 days
- PEPSE should not be considered or encouraged as a first-line method of HIV prevention. Other more evidence-based methods should be discussed
- We recommend the use of Truvada and raltegravir as the regimen of choice for PEPSE

PEPSE

UK Guideline for the use of HIV Post-Exposure Prophylaxis Following Sexual Exposure (PEPSE) 2015

How it (might) works

- Pathogenesis studies indicate that there may be a window of opportunity to avert HIV infection by inhibiting viral replication following an exposure
- Once HIV crosses a mucosal barrier it may take up to 48–72 hours before HIV can be detected within regional lymph nodes and up to five days before HIV can be detected in blood
- Initiation of antiretroviral therapy (ART) has been shown to reduce dissemination and replication of virus in all tissues if initiated early after inoculation in an animal model

Risks v benefits

Factors that increase risk

1. A high plasma HIV viral load (VL) in the source
2. Breaches in the mucosal barrier
3. Menstruation or other bleeding – theoretical risk only
4. Sexually transmitted infections in HIV positive individuals not on ART or HIV negative individuals with genital ulcer disease
5. Ejaculation
6. Non-circumcision - circumcision has been shown to significantly reduce HIV acquisition among heterosexual men in high prevalence countries
7. Discordant HIV viral load in the genital tract
Summary table of PEPSE prescribing recommendations (aka ‘what you might do and who you might do it with’)

<table>
<thead>
<tr>
<th>HIV VL unknown / detectable (&gt;200 copies/ml)</th>
<th>HIV VL undetectable (&lt;200 copies/ml)</th>
<th>Risk from high prevalence country / risk group</th>
<th>Risk from low prevalence country / risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptive anal sex</td>
<td>Recommend</td>
<td>Not recommend</td>
<td>Recommend</td>
</tr>
<tr>
<td>Insertive anal sex</td>
<td>Recommend</td>
<td>Not recommend</td>
<td>Recommend</td>
</tr>
<tr>
<td>Receptive vaginal sex</td>
<td>Recommend</td>
<td>Not recommend</td>
<td>Recommend</td>
</tr>
<tr>
<td>Insertive vaginal sex</td>
<td>Consider</td>
<td>Not recommend</td>
<td>Recommend</td>
</tr>
<tr>
<td>Fellatio with ejaculation</td>
<td>Not recommend</td>
<td>Not recommend</td>
<td>Not recommend</td>
</tr>
<tr>
<td>Fellatio without ejaculation</td>
<td>Not recommend</td>
<td>Not recommend</td>
<td>Not recommend</td>
</tr>
<tr>
<td>Splash of semen into eye</td>
<td>Not recommend</td>
<td>Not recommend</td>
<td>Not recommend</td>
</tr>
<tr>
<td>Cunnilingus</td>
<td>Not recommend</td>
<td>Not recommend</td>
<td>Not recommend</td>
</tr>
<tr>
<td>Sharing of injecting equipment</td>
<td>Not recommend</td>
<td>Not recommend</td>
<td>Not recommend</td>
</tr>
<tr>
<td>Human bite</td>
<td>Not recommend</td>
<td>Not recommend</td>
<td>Not recommend</td>
</tr>
<tr>
<td>Needlestick from a discarded needle in the community</td>
<td>Not recommend</td>
<td>Not recommend</td>
<td>Not recommend</td>
</tr>
</tbody>
</table>

BHIVA statement use of antiretroviral therapy to reduce HIV transmission

There is now conclusive randomized clinical trial evidence, from discordant heterosexual couples, that if the partner who is HIV positive is taking effective ART, transmission of HIV through vaginal sex is significantly reduced.

It is recommended that health care professionals discuss with all people living with HIV the impact of ART on the risk of transmission to sexual partners.

No single prevention method can completely prevent HIV transmission. ART reduces the risk of transmission only of HIV. Irrespective of ART, condoms remain the most effective way to prevent the spread of other STIs.

TasP (Treatment as Prevention)

HIV prevention methods that use ART in HIV+ persons to decrease the chance of HIV transmission

https://whqlibdoc.who.int/hq/2012/WHO_HIV_2012.12_eng.pdf?ua=1

HIV Medicine (2013), 14, 259–262