HIV/AIDS: basics and prevention

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Topics of the talk

• Basics of HIV and its biology
• Basics of HIV/AIDS
• Epidemiology & impact
• Clinical course and pathogenesis
• Diagnostics and Treatment
• Origin & variability
• HIV Prevention & Vaccine development
In 1981 a new clinical syndrome was described among young American homosexual men.

- Presented as immune deficiency
- AIDS = Acquired Immune Deficiency Syndrome
- Causative agent discovered in 1984 = Retrovirus
• HIV: Human Immune Deficiency Virus = the virus

• AIDS: Acquired Immune Deficiency Syndrome ~ the disease caused by the virus
• Sexual

• Direct blood contact (transfusions, sharing needles)

• Vertical (mother to child)
HIV-infection and AIDS

• HIV-infection
  – Virus infection, infected individual remains asymptomatic for long time even without treatment (2-20 years)
  – Infectious for life

• AIDS
  – The final, symptomatic stage of the development of HIV-infection: immune failure, opportunistic infections
What is HIV?

- HIV is a lipid-membraned RNA-virus (retrovirus) which causes a lifelong, chronic infection
- There is still no cure for HIV-infection, but treatment has tremendously improved
• HIV
• + strand diploid RNA-virus
• Cap- and poly-a in genome
• Lipid enveloped (most)
• Capsidi- and core structure
• RT i.e. reverse transcriptase
• DNA-form as integrated provirus
Retrovirus family

- Genus: "Mammalian type B retroviruses"
- Genus: "Mammalian type C retroviruses"
- Genus: "Avian type C retroviruses"
- Genus: "Type D retrovirus group"
- Genus: "BLV-HTLV retroviruses"
- Genus: Lentivirus
- Genus: Spumavirus
Retroviral lineages based on pol sequence
Virus particle approx 100 nm

- **Envelope**: (gp120 and gp41, lipid bilayer)
- **Core**: (RNA, NCp7 P6)
- **Protease**: RT
- **Integrase**: 
- **Capsid**: (p24)
- **Matrix**: (p17)
EM: HIV-particle

Envelope (gp120 and gp41, lipidbilayer)

Core
Attachment, entry, reverse transcription and integration
Heterodimeric p55/p65
Active polymerisation site and
RNAse H activity
Expression, assembly, budding and maturation
Epidemiology and impact
UNAIDS Global estimates

Adults and children estimated to be living with HIV/AIDS as of end 2004

Total: : 39.4 (35.9 – 44.3) million
HIV infections newly diagnosed:

Cases reported in 2004 per million population
WHO European Region

* Estimate based on data for half a year
NA: data not available
HIV infections newly diagnosed per million population by year of report (1994-2004) and geographic area
WHO European Region*

* Countries excluded (data not available for the whole period):
  West: Andorra, Austria, France, Italy, Malta, Netherlands, Norway, Portugal, San Marino, Spain;
  Centre: Bulgaria, Croatia
HIV infections newly diagnosed per million men and women, by geographic area, 1994-2004
WHO European Region*

* Countries excluded (data not available for the whole period):
West: Andorra, Austria†, France†, Italy†, Malta†, Netherlands†, Norway, Portugal†, San Marino, Spain†;
Centre: Bulgaria, Croatia
HIV infections newly diagnosed per million population 1994-2004, selected countries, eastern Europe

Cases per million

Year of report

Ukraine
Latvia
Belarus
Russian Federation
Estonia

Update at 31 December 2004
Newly reported HIV cases in Finland

- **MSM**
- **Heterosexual**
- **IDU**

- **not reported**


Cases reported:
- 0
- 10
- 20
- 30
- 40
- 50
- 60
- 70
- 80
- 90
Clinical course and pathogenesis
Immune deficiency = Symptomatic disease

AIDS

Clinical course of HIV infection w/o ARV treatment

Time: 5-20 y

T4 helper cells

Primary infection

Viremia (viral load, i.e. RNA copie/ml)

viral load set point

Death

Immune deficiency = Symptomatic disease
AIDS
Plate G: Relationship between viral load and prognosis in patients

Relationship of viral load and disease progression
• Loss of CD4+ helper lymphocytes -> Immune deficiency, opportunistic infections
CD4+ T-cells (T4-cells) normal function

APC

MHC-II

Peptide antigen

TCR

CD4

T4

Th1 & Th2 response activation
Loss off CD4+ Helpers: leaking bucket model

- Newly produced cells
- Healthy immune system
- Killed cells
Loss of CD4+ Helpers: leaking bucket model

- Newly produced cells
- Damaged immune system
- Killed cells
Loss off CD4+ Helpers: leaking bucket model

- Newly produced cells
- SICK immune system
- Killed cells
HIV dynamics

- Cell particle production $10^2$
- Daily replication cycles $10^7$
- Daily particle production $10^9$
- HIV genome size $10^4$
- RT error freq. $10^{-5}$/base

-> all mutations occur daily

-> virus exists as swarm, quasispecies

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HIV-diagnostics
HIV laboratory diagnostics

- Mainly based on indirect evidence of HIV-infection
- Detection of antibodies targeted to virus
- Screening (EIA and rapid tests)
- Confirmatory antibody tests (Western-blot)
- PCR only direct test
Serologic markers post-infection

- IgG
- IgM
- HIV-Ag

Weeks after infection
**HIV-antibody tests**

- I, II, III- generation ELISA-tests
  - I = Ag viruslysate -> unspecific reactions
  - II = Ag recombinant proteins
  - III = Ag synthetic peptides

- Rapid tests

- Confirmation (Western-blot)
**Screening**

- Negatiivinen
  - Vastaus Ei-HIV vasta-aineita
- Positiivinen
  - Uusinta testi positiivinen
  - Uusinnoissa toistettavasti negatiivinen
  - Vastaus Ei-HIV vasta-aineita

**Confirmation**

- Negatiivinen
  - Vastaus Ei-HIV vasta-aineita
- Positiivinen
  - Pyydetään uusi näyte
  - Epäselvä
  - Vastaus HIV-vasta-aine positiivinen
  - Prosessin alkuun
Detecting HIV infection (1)

- Antibody tests detect
  - Evidence of infection on average 2.1 months post-infection
  - After 3 months 97% or more of all infections detected
  - Detect both HIV-1 and HIV-2 infection
  - Infected remain antibody positive for life
Treatment of HIV-infection
• VIRUS-infection
  – combination drug treatment

• Opportunistic infections:
  – if symptoms of immune deficiency develop (=AIDS)
ARV goal: stop replication of virus

- Helper T-lymfocytes
- Viremia

HAART

- Viral load and CD4+ helper cell counts directly correlated to likelihood of developing AIDS
- Goal of therapy -> as complete suppression of virus replication as achievable
Selective Pressures of Therapy

Time

Viral load

Drug-susceptible quasispecies
Drug-resistant quasispecies

Treatment begins

Selection of resistant quasispecies

Incomplete suppression
- Inadequate potency
- Inadequate drug levels
- Inadequate adherence
- Pre-existing resistance
Drug resistance may develop despite ART

- **Particles produced per day** $10^9$
- **HIV genome** $10^4$
- **Error rate of RT** $10^{-5}$/d

-> All single point mutations occur every day

-> Virus exists as swarm or quasispecies

-> Drug resistance may develop rapidly in individual patient
Drug Resistance: Selection Pressure(s)

- **Drug A Pressure**
  - "wild" type virus (drug susceptible)
  - "mutant" virus (1X drug resistant, cross resistance?)

- **Drug A + B Pressure**
  - "mutant" virus (2x drug resistant, cross resistance?)

**VIRAL LOAD**

**TIME**
Combined use of Anti-HIV Drugs

VIRAL LOAD

Drug Pressure A
Drug Pressure B
Drug Pressure C ...

○ Functionally disabled HIV

TIME
Multi-drug continuous combination treatment

- **Nucleoside RT inhibitors NRTI**
  - AZT
  - ddC
  - ddl
  - d4T
  - 3TC
  - ABC
  - TNV
  - FTC
  - Hydroxyurea

- **Non-nucleoside RT inhibitors NNRTI**
  - Nevirapine
  - Delavirdine
  - Efavirents

- **Protease inhibitors PI**
  - Indinavir
  - Saquinavir
  - Nelfinavir
  - Ritonavir
  - Amprenavir
  - Lopinavir

Also: new drugs and drug classes in development
• Two targets in virus:
  – Reverse transcriptase, RT
  – Protease
Nucleoside analogues - NRTI

AZT, ddI, ddC, d4T
Non-Nucleoside analogues - NNRTI

Nevirapine
Fusion inhibition
Effect of HAART
Mortality in patients with CD4<100 of antiretroviral (ARV) therapy including a protease inhibitor among those patients, USA, 1994–1997

Source: Palella et al., New England Journal of Medicine, 1998 Mar, 26:338–60

Note: For comparison with data for 1999-2000, data for 1987-1998 were modified to account for ICD-10 rules instead of ICD-9 rules.

†Preliminary mortality data for 2000.
Number of deaths among HIV-infected patients

Deaths / 100 patients

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Life of an HIV-infected person today...

- follow-up without HAART until CD4 ~ 300
  - vaccinations, gynecologist, dentist
  - start HAART with 3 antiretrovirals at outpatient clinic
- lifetime prognosis?? tens of years??
  - organ transplants
- education, work, family, pregnancies…
Eradication? Latent reservoir...
Dynamics on HAART

Plasma HIV-1 RNA (copies/mL)

First phase ($t_{1/2} = 1$ day)

Second phase ($t_{1/2} = 14$ days)

Third phase? ($t_{1/2} = ?$)

Limit of detection

Time on HAART (days)
HIV/AIDS prevention
HIV prevention

• Challenges leading to stigma and discrimination
  – Sexual and blood-borne transmission
  – Frequent association to often non-accepted phenomenons (MSM & other minorities, IDU etc.)
  – Chronic, incurable infection
  – Long asymptomatic phase with
  – Very expensive treatment -> access very incomplete

• Tools
  – Biomedical (?)
  – Technical
  – Knowledge and behaviour change
Vulnerability to HIV infection

• Large variations globally
  – "West" US/Canada & Old-EU: long domination of higher rates of transmission among population subgroups: MSM & sexual minorities, IDU, sexworkers, some indigenous minorities and immigrants/migrants.
  – Developing world: heterosexual transmission dominates, BUT equally high vulnerability among vulnerable groups
  – New phenomenon (last 10 y): transition & growing economies: Russia, Baltic states, China, India -> major vulnerabilities associated with IDU and sexwork

• Special concerns
  – Mother to child transmission
  – Transfusion & blood product associated transmission
Prevention strategies

• Necessary to adapt to epidemiological setting, but basic principles generally similar throughout the world
  – Sexual transmission: easy in theory, tremendously challenging in practice
  – Blood borne transmission: partially addressably by technical precautions but IDU prevention challenging
  – MTCT: preventable to 99 %
• HIV prevention is NOT simply a medical issue: it’s complicated by challenges in basic knowledge, understanding, misconceptions, behaviour and fear of stigma and discrimination

• Prevention can be divided into Primary and Secondary prevention i.e.:
  – Prevention among those who are not infected
  – Prevention among those who have the infection
Primary prevention

• MTCT
  – By treatment prophylaxis prior and at delivery and abstaining from breastfeeding transmission levels can be reduced from >25% to <1%
  – Need to know HIV status of mothers -> screening programme (opt-out) in Finland for mothers

• Blood products
  – Always screen
Primary prevention

• Drug Use

• Sexual Transmission
  – Challenging: condom use and risk reduction needed, but behaviour change is not easy
  – Knowledge does not automatically turn into action
Acknowledging the facts

- Injecting drug use in itself is not the cause of the frequently seen Hepatitis and HIV epidemics among drug users
- The real problem is sharing of the same injection equipment and paraphernalia used to prepare drugs
- Sharing exposes users to exchanging not only the equipment, but inadvertently also blood
- If you can prevent the sharing, the viruses have no way of spreading

- The most common reason for sharing is the lack of access to clean (i.e. Sterile) equipment
Policy implementation

- Establishment of a Network of Low Threshold Health Service Centers (LTHSC) for IDU in Finland
  - Trust-based function: voluntary, not based on being drug-free, personal information not recorded
  - Close and accessible to target group
  - Services include small-scale healthcare provision, counselling & guidance to detoxification, VCT & HIV-testing, vaccinations (tetanus, HBV, HAV), condom distribution and exchange of injection equipment
  - Base for outreach work among IDU
  - Close collaboration with detox- and primary health care services, social services and law enforcement
Equipment for exchange
Syringe and needle types
Tests and Vaccinations
Vinkissä on kiellettyä:
- uhkailla tai käyttäytyä väkivaltaisesti
- selvitellä velkoja tai muita erimielisyyksiä
- käyttää päihteitä tai lääkkeitä
- käydä kauppaa

- No violence
- No threats
- No using
- No dealing
Information and training
Service information
Drug users – targeted information – reach the population

Kesällä on todettu huumeiden käyttäjiä Suomessa saatuja HIV-tartuntoja.

Puhtaat välineet

Jäsäntä on päätέänkii seudulla todettu

HIV-tarttuminen

Kesällä on todettu huumeiden käyttäjiä

Suomessa saatuja HIV-tartuntoja.
Policy change implementation

- Network of Low Threshold Health Service Centers (LTHSC) for IDU in Finland
- 1997: 1 site in Helsinki
- Scale-up of network coverage during 1997-2005
• **Law on communicable diseases 25.7.1986/583** (with changes 2004)
• **Ordinance on communicable diseases 31.10.1986/786**
• **6 §** ....The municipal authority responsible for communicable disease control and as its subordinate, the municipal health care physician responsible for communicable diseases, must as a task specified by the Law on Communicable Disease also:

1) Organise communicable disease control activities in the municipal health care area, such as communicable disease information distribution, health education and health advice, including health advice services and exchange of injection equipment for injecting drug users as specified by the need for communicable disease control.
HIV, HCV – prevalence, unlinked anonymous in LTSC

Prevalence (%)

Year

1998 2001 2002 2003 2004 2005

HCV

HIV
Newly reported HIV-cases in Finland (IDU)
Secondary prevention

• **Need to know your status**
  – Low threshold to testing services
  – VCT: principle of voluntary counselling and testing
  – Access to treatment essential incentive