Prognosis without ART: interplay between quantity of CD4 and HIV-RNA

3-year probability of AIDS in 1604 men enrolled in the Multicenter AIDS Cohort Study (MACS) 1984-1985

Number of drugs in ART across Europe: 1994-1998

Relative hazard of death

EuroSIDA

adjusted for use of therapy

not adjusted for use of therapy


Swiss HIV Cohort Study: Ledergerber et al, BMJ 1999
Discontinuation of Secondary PCP Disease-Specific Chemoprophylaxis After Immunological Recovery

- Start of Potent Antiretroviral Therapy
- Discontinuation of Secondary Prophylaxis

- Persons: 325
- Median follow-up time: 13.2 months (7.0-19.0)
- Person-years of follow-up: 374.5
- Recurrent PCP: 0
- Incidence: 0 (0-1.23)* per 100 person-years

Diagnosis of *Pneumocystis jirovecii* Pneumonia

*Ledgergerber. NEJM 2001.*
Resistance of *Pneumocystis jirovecii* to sulfa-drugs: 3 month mortality from date of diagnosis of PCP

Survival Functions

- **Wildtype**
- **Dihydropteroate synthase (DHPS) mutations**

Helweg-Larsen et al. Lancet 1999;354:1347
Enthusiasm for an agent as a function of time since first introduced

Time since initiation of phase I trials (years)

Textbook in Pharmacology, 1960’s
Example of toxicity “missed” in “official” system

- Abnormal fat distribution
  - 1995-97: Randomised trials evaluating efficacy/ toxicity of ARVs. Lipodystrophy not identified
  - Feb. ‘98: First report, Carr et al. (cohort study)
  - March ‘99: EMEA initiative (product labelling)
  - 2003: stavudine (and less so zidovudine) responsible
How best to address toxicity's of anti-HIV drugs in 1999

- Early onset of common event
  - Phase I/II/III trials
- Early onset of rare event
  - Meta-analysis of data from randomised trials
- Late onset of common event
  - Cohort studies (large size will increase power) and long-term randomised trials
- Late onset of rare event
  - Large size cohort studies and long-term randomised trials
Antiretroviral drugs and risk of myocardial infarction

MIs per 1,000 PY (95% CI)

Test for trend
p<0.00001

Prevalence of hepatitis

EuroSIDA: Soriano et al, JID 2002
HIV epidemic in eastern Europe and central Asia the fastest growing in the world:

Estimated number of people living with HIV in WHO European Region, 1990-2011

The number of new cases of HIV infection in Russian citizens, 1987 - 2009

*: numbers continue to increase in 2010/11 (app 70,000)
20-25 million HIV tests per year – www.hivrussia.org

UNAIDS Country Report
Infection increasing faster than treatment: WHO European Region, 1985–2011

Lack of engagement/retention in care/initiation of cART

Delpech V. BHIVA Conference, 2013
Treatment cascade in Europe

- Infected
- Diagnosed
- In care*
- On ART
- Fully suppressed

*: incomplete data on number of persons in care in Eastern Europe
Durability of HIV suppression*: the key indicator to benchmark for good ART care varies by 40% across Europe

Proportion of FU where >90% FU has VL < 500

Region:
- North
- Cen/W
- Cen/E
- South
- East

*: % of follow-up (FU) on ART where >90% FU has VL < 500
Retention in care require health systems to manage all aspects of care: poor opioid substitution therapy (OST) coverage in EE*

<table>
<thead>
<tr>
<th>Country</th>
<th># IDU</th>
<th>% of IDU receiving OST</th>
<th># IDU HIV+ in 2010</th>
<th># of HIV+ IDU on ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belarus</td>
<td>75,000</td>
<td>0.3%</td>
<td>10,500</td>
<td>?</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>186,000</td>
<td>0.1%</td>
<td>5,580</td>
<td>182</td>
</tr>
<tr>
<td>Lithuania</td>
<td>5,458</td>
<td>?</td>
<td>1,250</td>
<td>62</td>
</tr>
<tr>
<td>Moldova</td>
<td>25,000</td>
<td>1.4%</td>
<td>4,450</td>
<td>446</td>
</tr>
<tr>
<td>Russia</td>
<td>2 million</td>
<td>0%</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Ukraine</td>
<td>375,000</td>
<td>2.1%</td>
<td>85,000</td>
<td>1732</td>
</tr>
</tbody>
</table>

15.9 million IDU’s globally – 80% in low-middle income countries

*: OST coverage in Western Europe: 30-60%

Petersen et al. Harm Reduction J, 2013
Mortality after TB in HIV+ remains high in Eastern Europe (EE) but decreases markedly in Western Europe/Argentina (WEA).

Main reasons:
- Most TB is MDR/XDR
- TB tx uncoordinated
- Poor retention in care
- = no ART

TB remains leading cause of deaths among HIV+ in EE

Podlekareva et al, ERJ 2013
Potential impact of cART on epidemic

Granich RM et al. Lancet 2009
Potential impact of cART on epidemic

In MSM communities across Western Europe:

- Increasing ART coverage
- More condom-less sex
- Increasing HIV incidence

ART coverage – what is the target % required to get reproductive rate < 1?

When to START ART?

Benefit to
Individual vs individuals sexual partner vs societal benefit
Natural history of HIV: CD4 count distribution according to time from infection
Guidelines Change but not in Synchrony

De Cock & El-Sadr, NEJM 2013
Survival after ART initiated at different CD4 count levels between 200-500: "causal" modelling

**Implication**
Randomized, controlled trials are needed to better define the optimal time of initiation of combined antiretroviral therapy in HIV infection.

—*The Editors*
The choice to make for asymptomatic treatment naïve patients

Talk in 2003
Use of more stringent criteria, such as those proposed by the GRADE approach, would likely reach the conclusion that the evidence is insufficient to make firm recommendations [for starting ART at CD4 of 500 vs deferring to 350 cells/µL].
### Major Guidelines for ART Initiation

<table>
<thead>
<tr>
<th>Guideline</th>
<th>AIDS or HIV-Related Symptoms</th>
<th>CD4+ Cell Count &lt; 200/mm³</th>
<th>CD4+ Cell Count 200-350/mm³</th>
<th>CD4+ Cell Count 350-500/mm³</th>
<th>CD4+ Cell Count &gt; 500 cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHHS-USA, 2013</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes⁴</td>
<td>Yes²</td>
</tr>
<tr>
<td>International AIDS Society-USA, 2012</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes¹</td>
<td>Yes²</td>
</tr>
<tr>
<td>British HIV Association, 2012</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Defer³</td>
<td>Defer³</td>
</tr>
<tr>
<td>European AIDS Clinical Society, 2013</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Consider³</td>
<td>Consider³</td>
</tr>
<tr>
<td>World Health Organization, 2013</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Consider⁴</td>
<td>Defer⁵</td>
</tr>
</tbody>
</table>

(1) Strong strength recommendation based on observational data (A-II)
(2) Moderate strength recommendation based on expert opinion (B-III).
(3) But treat all HIV+ pregnant women, HBV co-infection, HCV co-infection, HIVAN, HIV related neurocognitive disorders, ITP, non-AIDS cancers and serodiscordant couples

(4) But treat individuals with CD4 < 350 a priority.

(5) But treat all HIV+ pregnant women, TB co-infection with active disease and HBV co-infection with severe liver disease, and serodiscordant copuls
Late presentation by year of presentation

**Proportion**

- **LP:** CD4 < 350/AIDS
- **advanced immunodeficiency:** CD4 < 200/AIDS

**Median CD4 at presentation**

- Crude odds ratio 0.96 (0.95 – 0.97) per calendar year
- Crude odds ratio 0.95 (0.94 – 0.96) per calendar year
- Crude odds ratio 0.94 (0.93 – 0.95) per calendar year
- Crude 4.4 (3.8 – 5.0/mm³) per year increase in CD4 at presentation

CD4 count recovery on ART if fully virally suppressed

Based on a random effects model

UK CHIC Study; Hughes et al, HIV Medicine 2010; see also Mocroft et al Lancet 2007
CD4 count and risk of non-AIDS disease events in people on ART with viral suppression: D:A:D

Rate ratio

Liver
Non-AIDS Cancer
Renal
Stroke
MI

Trend highly statistically significant in all cases except for MI

Frailty in treated HIV infection associated with elevated levels of T cell activation, (the classic geriatric syndrome) IL-6, CPR, TNF-alpha and sCD4

Erlandson, JID 2013
A single measurement of IL-6 or D-dimers predicts morbidity or mortality over next decade.
Is resistance likely to be a problem?

Time to virological failure (bold line) and >1 IAS mutation (dotted line) after starting cART - UK CHIC/UK HDRD

Prevalence of transmitted drug resistance over time, stratified by drug class - UK HDRD

\[1\] Cozzi-Lepri A et al. CID 2010; \[2\] Dolling D et al. BMJ 2012
### Changing natural history?: Impact of year of seroconversion on viral load setpoint and CD4 loss

<table>
<thead>
<tr>
<th>Year</th>
<th>Viral load set-point (log&lt;sub&gt;10&lt;/sub&gt; cps/ml)</th>
<th>CD4 loss (cells/mm&lt;sup&gt;3&lt;/sup&gt; per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>95% CI</td>
</tr>
<tr>
<td>1996-99</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2000-03</td>
<td>0.12</td>
<td>(0.02, 0.23)</td>
</tr>
<tr>
<td>2004-05</td>
<td>0.15</td>
<td>(0.03, 0.26)</td>
</tr>
<tr>
<td>2006+</td>
<td>0.01</td>
<td>(-0.09, 0.12)</td>
</tr>
</tbody>
</table>
Unanticipated association between abacavir use and raised risk of myocardial infarction
Abacavir, a Competitive Inhibitor of Guanylyl Cyclase (sGC), Increases Platelet Reactivity

Nitric Oxide

- sGC
- GTP
- cGMP

Inactive platelet

Increased platelet activity
Increased MI risk

Abacavir

Baum et al, JID 2011
The excess risk of CAD in HIV disease increases with age, suggesting that problems will become more apparent in the next decade.

RR adjusted for age, gender, race, hypertension, diabetes, and dyslipidaemia.

*Triant VA et al, J Clin Endocrinol Metab, 2007*
Proportion of patients on anti-CVD medication
1st January each year

Proportion on CVD medication (95%)
ART exposure and AIDS- and non-AIDS-defining cancer

AIDS-defining cancer (n = 1,151)

Non-AIDS-defining cancer (n = 1,091)

Adjusted for age, sex, cohort, HIV mode of acquisition, ethnic group, calendar year, body mass index, any prior cancer, prior AIDS diagnosis, prior AIDS cancer, smoking status, HCV and HBV status

Depressive symptoms and current treatment for depression

<table>
<thead>
<tr>
<th>PHQ-9 Depressive Disorder status</th>
<th>Current treatment for depression?*</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ-9 DD (N=579)</td>
<td>YES</td>
<td>241</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>338</td>
</tr>
<tr>
<td>No PHQ-9 DD (N=1596)</td>
<td>YES</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>1396</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>2175</td>
</tr>
</tbody>
</table>

*Medicine or other therapy for depression

- Total prevalence of depression (treatment or symptoms): 35.8% (779/2175)
- Among those with evidence of depression, 43.4% (338/779) were not receiving any treatment for depression

ASTRA study: Lampre et al, BHIVA, 2012
Cure success in HCV: the era of direct-acting antivirals (DAAs)

Treatment uptake across Europe:
- 25% of HIV/HCV co-infected were treated
- 22% of untreated had F2 or more
- 36% of treated had F2 or more

EuroSIDA Grint et al. HIV Medicine 2013

*In patients with HCV genotype 1; ** In treatment-naïve patients; IFN, interferon; RBV, ribavirin; SVR, sustained virologic response

Challenges in care when DAA becomes standard-of-care treatment for HCV

- Will likely be expensive
- Most pivotal trials done in persons with F0-F1
  - F3/F4 stand to benefit the most but also more ADR – avoid repeat of problems w/ 1st generation PI’s

<table>
<thead>
<tr>
<th>Factors</th>
<th>Platelet count &gt;100,000/mm³</th>
<th>Platelet count ≤100,000/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum albumin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥35 g/L</td>
<td>3.4% (10/298)</td>
<td>4.3% (3/69)</td>
</tr>
<tr>
<td>&lt;35 g/L</td>
<td>7.1% (2/28)</td>
<td>44.1% (15/34)</td>
</tr>
</tbody>
</table>

Hézode et al. J Hepatol 2013

- Eastern Europe: app 800,000 HIV+/HCV+
  - access projected low – priority on ART earlier
Quality of care:

Define settings implementing best standard of care

Benchmark own performance (by use of indicators of care)

Degree of insufficient care (not poor vs good care) so targeted approach to improve care
Strengths and challenges within Europe to provide “good” care for HIV+ persons

**Strengths**

- When working well HIV care is very good (optimal?)
  - experienced clinics w/ broad availability of medicine + no/minimal fee for care

**Challenges**

- Financial and political “instability” – erosion of good standard
- Public health policies sometimes contra-productive
  - e.g. not wise to exclude diagnosed HIV+ from care
- Available evidence - diversity in quality
  - Linkage and retention in care
  - Medicines for HIV, coinfections, comorbidities, addiction
- Need for continent-wide benchmarking of quality to find “hot-spots” of good and poorer care
Task shifting

• If we don’t figure it out – funders of health systems will

• In countries using
  • public health approach to care:
    • From doctors to nurses to assistants to community
    • Well integrated (out of necessity often) and evidenced based
  • Individualized care:
    • In stable well-treated HIV+ person – risk of viral failure is low
    • Interval between visits to HIV clinic progressively longer
    • General practitioners progressively involved with care
      – Define roles and responsibilities
      – Who is overall responsible for care
      – How to delegate responsibilities for component of care?
      – How to oversee quality of care?
Future: paradigm shift in HIV care

• Considerations
  • HIV care requires experience and high case load
  • Countries will centralized care have high retention and durable suppression rates
  • Task shifting could erode this success

• HIV specialist oversee care in “uncomplicated” patients provided by
  • General practitioners
  • Nurses in “own” outpatient clinic (physically located either within medical facility or in community)
  • Email clinic in Brigton (Whetham et al, EACS PS8/6)
    • electronic surveillance flagging abnormal course of follow-up
Summary

• Cohort studies instrumental to understand risk and benefits from ART
  • Consequences of lack of use of ART
  • Balance discussion on public health use of ART prevention
  • “Misused” in contemporary discussion on WTS

• Future role
  • Transmission and prevention
  • Issues from longer use of ART (good or bad)
  • Pathogenesis and host-response – biobank incl host DNA
  • Rational use of DAA for HCV
  • Best handling of emerging MDR/XDR TB
Acknowledgements

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- J Rockstroh, G Faetkenheuer
- EuroSIDA for EuroCoord colleagues last 20 years