Clinicopathological Conference at the Annual Workshop in Advanced Clinical Care, Durban
October 1, 2010

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Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban

Quarraisha Abdool Karim PhD
Centre for the AIDS Programme of Research in South Africa (CAPRISA)
Differential Diagnosis

Prof WD Francois Venter, FCP (SA)

Senior Director
The Institute
Associate Professor, Department of Medicine
University of the Witwatersrand,
Johannesburg, South Africa
In summary

• 19 year old woman in KZN, socially representative, not using contraception/condoms
• Headache, fatigue, loss of appetite, resolved after 2 weeks
• Vaginal discharge, then a painful genital ulcer (RPR and HIV negative) with lymphadenopathy
Important in medicine

Differentiate between:

• What you need to know for exams / what you’ll see in the clinicals
• What you need to know as a doctor
  - the diagnosis its fun to make
  - the diagnosis you will make
  - the diagnosis you must never miss
* Haemorrhagic fever vs a cold
Missing from history & examination

- Travel history – I am assuming there isn’t one
- More details on ulcer
Differential diagnosis

• Vaginal discharge vs ulcer vs constitutional symptoms/ adenopathy
• Very, very wide – what DOESN’T cause headache, fatigue, loss of appetite?
• But: common things commonly
Could the STD explain her constitutional symptoms?

• YES
• Other causes with lymphadenopathy: viraemias, other infections, connective tissue diseases, sarcoid, neoplasms,
Infections…

- Linked to STD: syphilis, hepatitis B or C, HIV, CMV
- Streptococcus
- TB
- Toxoplasmosis
- Schistosomiasis
- Rubella, EBV, cat scratch disease, infective endocarditis, bubonic plague, typhoid, brucella, leptospirosis, abscesses, typhus, …
- Geography against range of others: Lymes, kala-azar, trypanosomiasis, histoplasmosis (and other fungal infections)…
- And lots of others
- Neoplasms? Unlikely
- CTD/ sarcoid/ Takayasus/ Kawasaki? Unusual
Medications

• Medication associated with lymphadenopathy: Antibiotics (penicillin, suphonamides, cephalosporins), antihypertensives (captopril, atenolol, hydrlazine), phenytoin, others

• Alternative medication/ traditional healer
Let's talk about the STD
Background on STDs

• High prevalence and incidence of STDs
• Gauteng >600 000/ 10 million new STDs in 2002
• Males – urethritis 70%, GUD 20%
• Females – Vaginal discharge 70%, PID 12% and GUD 15%.
Discharge?

• Clinical assessment poorly correlated with specific diagnosis
Vaginal discharge syndrome

• Abnormal discharge → what is “abnormal”?

• Foul smell → what is “foul”?

• Vulval itching

• Dysuria
Discharge appearance

- “clear”/watery
- homogenous, greyish
- purulent
- frothy
- curdy
Vaginal discharge syndrome

- Cervical discharge
- Vaginal discharge
- Urethritis
Causes of cervical discharge

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- *(Mycoplasma genitalium)*
Causes of vaginal discharge

- *Trichomonas vaginalis* → STI
- Bacterial vaginosis → ? STI
- Vaginal candidiasis → no STI
Prevalence (%) of discharge aetiology among women attending primary health clinics in rural KwaZuluNatal in 2000

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total (n=744)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bacterial vaginosis</td>
<td>66</td>
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<tr>
<td><em>T. vaginalis</em></td>
<td>28</td>
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<tr>
<td><em>N. gonorrhoeae</em></td>
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<tr>
<td><em>C. trachomatis</em></td>
<td>10</td>
</tr>
<tr>
<td>candidiasis</td>
<td>1</td>
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</table>
Discharge appearance: typical for causative agent?

- “clear”/watery  → physiological
- homogenous, greyisch  → bacterial vaginosis
- purulent  → gonococcal
- frothy  → trichomonas
- curdy  → candida
Genital ulcers

• Medical history and examination often inaccurate
## Genital ulcer disease (GUD)

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<thead>
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<th>Disease</th>
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Remember: Immune competent… - in HIV, can be a range of things…. 

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<th>Region</th>
<th>Herpes</th>
<th>Syphilis</th>
<th>LGV</th>
<th>Chancroid</th>
<th>Donovanosis</th>
<th>No Aetiology</th>
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</thead>
<tbody>
<tr>
<td>Northern Cape 2006</td>
<td>63</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>Mpumalanga 2006</td>
<td>46</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>51</td>
</tr>
<tr>
<td>Gauteng 2007</td>
<td>53</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Western Cape 2007</td>
<td>33</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>53</td>
</tr>
</tbody>
</table>

STI Reference Centre, National Institute for Communicable Diseases
Syphilis rates, 2008 antenatal survey, South Africa
Botswana Genital Ulcer Surveys

STI Reference Centre, National Institute for Communicable Diseases (2005 survey)
Botswana Ministry of Health

<table>
<thead>
<tr>
<th></th>
<th>1993 Survey</th>
<th>2002 Survey</th>
<th>2007 Survey</th>
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<tbody>
<tr>
<td>Herpes</td>
<td>35</td>
<td>61</td>
<td>65</td>
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<tr>
<td>Chancroid</td>
<td>33</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Syphilis</td>
<td>1</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>No Aetiology</td>
<td>54</td>
<td>39</td>
<td>32</td>
</tr>
</tbody>
</table>

N = 108, N = 137, N = 93
Decline of Chancroid in Miners
Carletonville, South Africa
(1986-1998)

Causes of Genital Ulcers in Carletonville Miners

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<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>chancroid</td>
<td>70</td>
<td>60</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>syphilis</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
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<tr>
<td>herpes</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>LGV</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

HSV by culture; LGV by culture + serology; chancroid by culture; syphilis by DGM + serology (FTA-Abs + RPR)

Ballard et al., former South African Institute for Medical Research
Disappearance of Chancroid from Nairobi


Year

Percent of ulcers HD positive

Men with ulcers
Sex workers with ulcers
Other

Source: STD Surveillance, Stephen
Specific diagnostics for GUD?

- Serologic test for syphilis
- Culture/antigen test for herpes simplex
- *Haemophilus ducreyi* culture
- Biopsy
Sexually Transmitted Infections (STIs):

- Ciprofloxacin 500mg stat per os.
- Doxycycline 100mg 1 BD x 7 days.
- Females: Add Metronidazole 2g stat per os (5 x 400mg tablets).
- Females: If pregnant – Erythromycin 500mg 4 times a day x 5 days.

Genital Ulcers:

- RPR
- Bicillen 8cc stat IM (2,4mu)
- Erythromycin 500mg 8 hourly x 7 days x 42.
What tests would help?

- Limited tests available at primary care especially for STD clients – syndromic approach generally effective
- HIV test generally available: negative
- Swabs, cultures, biopsies
- “Blind treatment” effective
What next?

• Well, she’s a KZN local…
HIV Prevalence by Age and Gender among SA youth age 15-24 years

Pettifor A, Rees H, et al. AIDS 2005
Figure 5: HIV prevalence distribution among antenatal women by province, South Africa 2008.
Table 6: HIV prevalence among antenatal women by district, KwaZulu-Natal, 2006 to 2008.

<table>
<thead>
<tr>
<th>District</th>
<th>2006</th>
<th></th>
<th></th>
<th>2007</th>
<th></th>
<th></th>
<th>2008</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% Prev.</td>
<td>CI (95%)</td>
<td>N</td>
<td>% Prev.</td>
<td>CI (95%)</td>
<td>N</td>
<td>% Prev.</td>
<td>CI (95%)</td>
</tr>
<tr>
<td>Provincial</td>
<td>6 814</td>
<td>39.1</td>
<td>37.5–40.7</td>
<td>6 918</td>
<td>38.7</td>
<td>37.2–40.2</td>
<td>6 963</td>
<td>38.7</td>
<td>37.2–40.1</td>
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<tr>
<td>Amajuba</td>
<td>400</td>
<td>46.0</td>
<td>41.1–50.9</td>
<td>404</td>
<td>39.3</td>
<td>34.3–44.6</td>
<td>420</td>
<td>34.7</td>
<td>29.2–40.7</td>
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<tr>
<td>Sisonke</td>
<td>229</td>
<td>31.9</td>
<td>25.8–37.9</td>
<td>328</td>
<td>34.1</td>
<td>29.3–39.2</td>
<td>343</td>
<td>35.8</td>
<td>31.6–40.3</td>
</tr>
<tr>
<td>Ugu</td>
<td>504</td>
<td>38.9</td>
<td>34.6–43.1</td>
<td>512</td>
<td>37.3</td>
<td>32.1–42.7</td>
<td>507</td>
<td>40.6</td>
<td>36.9–44.3</td>
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<tr>
<td>Umkhanyakude</td>
<td>410</td>
<td>36.3</td>
<td>31.7–41.0</td>
<td>407</td>
<td>39.8</td>
<td>34.3–45.5</td>
<td>413</td>
<td>39.9</td>
<td>34.8–45.3</td>
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<tr>
<td>Umzinyathi</td>
<td>319</td>
<td>27.9</td>
<td>23.0–32.8</td>
<td>338</td>
<td>31.6</td>
<td>26.2–37.6</td>
<td>339</td>
<td>29.2</td>
<td>23.7–35.2</td>
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<tr>
<td>Uthukela</td>
<td>459</td>
<td>35.1</td>
<td>30.7–39.4</td>
<td>452</td>
<td>36.2</td>
<td>29.5–43.6</td>
<td>450</td>
<td>38.6</td>
<td>32.6–45.0</td>
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<td>Uthungulu</td>
<td>566</td>
<td>34.6</td>
<td>30.7–38.5</td>
<td>567</td>
<td>35.9</td>
<td>31.0–41.2</td>
<td>641</td>
<td>36.1</td>
<td>31.4–41.2</td>
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<tr>
<td>Zululand</td>
<td>582</td>
<td>36.9</td>
<td>33.0–40.9</td>
<td>580</td>
<td>34.6</td>
<td>30.0–39.5</td>
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<td>36.1</td>
<td>31.8–40.5</td>
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<td>eThekwini</td>
<td>2 230</td>
<td>41.6</td>
<td>39.5–43.6</td>
<td>2 217</td>
<td>41.6</td>
<td>39.3–43.9</td>
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<td>37.4–43.0</td>
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<td>iLembe</td>
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<td>39.1</td>
<td>34.5–43.8</td>
<td>417</td>
<td>41.4</td>
<td>34.8–48.4</td>
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<td>44.4</td>
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<td>40.8</td>
<td>35.6–46.1</td>
<td>686</td>
<td>45.7</td>
<td>42.1–49.4</td>
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Prevalence of HIV Co-infection in STI Patients, South Africa

Data from 2006-2007

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<th>Province and Year of Survey</th>
<th>Vaginal Discharge</th>
<th>Male Urethritis</th>
<th>Genital Ulcer</th>
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<td>70</td>
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<td>58</td>
<td>54</td>
<td>71</td>
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<tr>
<td>Gauteng 2007</td>
<td>52</td>
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<td>75</td>
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<tr>
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<td>25</td>
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STI Reference Centre, National Institute for Communicable Diseases
STDs promote HIV transmission - biological plausibility

- STDs facilitate HIV shedding in genital tracts
- STDs recruit inflammatory cells to the genital tract
- STDs may disrupt mucosal barriers to infection
- Treatment of STDs reduces HIV viral shedding
Spiralling effect

• HIV effects STDs –
  – Immune suppression may promote STD acquisition
  – Immune suppression may promote STD persistence
  – HIV may promote STD transmission – by increased shedding of STD
  – Immune suppression increases HIV shedding
What are the chances this young woman had HIV? (conference none-withstanding)

• Without an HIV test: very likely
• BUT: we have several negative tests
HIV: Natural history

- Viral transmission
- Acute retroviral syndrome (2-3 weeks later)
- Recovery and seroconversion (2-3 weeks later)
- Asymptomatic chronic HIV infection (8 yrs)
- Symptomatic HIV infection/AIDS (1.3 yrs)
- Death
49-89% of patients “symptomatic” within 3 months...

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Schacker</th>
<th>Kinloch-de Loes</th>
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<tr>
<td>Fever</td>
<td>93%</td>
<td>87%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>93</td>
<td>26</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>70</td>
<td>48</td>
</tr>
<tr>
<td>Weight loss</td>
<td>70</td>
<td>13</td>
</tr>
<tr>
<td>Myalgias</td>
<td>60</td>
<td>42</td>
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<tr>
<td>Headache</td>
<td>55</td>
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Some evidence of less symptoms in Africa...
Laboratory Detection of HIV

Feibig, et al.  AIDS 2003

Symptoms (~60%)
p24 Antigen
HIV RNA
HIV Ab Tests

Weeks Since Infection
# Tests for early Infection

<table>
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<th>Assay</th>
<th>Test for:</th>
<th>window</th>
<th>Interval</th>
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<td>HIV RNA</td>
<td>Plasma RNA</td>
<td>RNA +</td>
<td>seroconversion</td>
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<tr>
<td></td>
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<td>15~20 days</td>
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<tr>
<td>HIV p24</td>
<td>Plasma p24</td>
<td>p24+</td>
<td>seroconversion</td>
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<tr>
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<td>~14 days</td>
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<td>STARHS</td>
<td>HIV Ab titer</td>
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<td>BED-CEIA</td>
<td>HIV Ab/total IgG</td>
<td>seroconversion</td>
<td>Ab proportion cutoff</td>
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<td>Avidity</td>
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<td>seroconversion</td>
<td>avidity cutoff</td>
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</tr>
<tr>
<td>Affinity</td>
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<td>seroconversion</td>
<td>affinity cutoff</td>
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<td>Variable</td>
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<td>IgG3 isotype</td>
<td>IgG3 anti-p24 Ab</td>
<td>seroconversion</td>
<td>undetectable IgG3 Ab</td>
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<td>~90 days</td>
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<td>anti-HIV p31</td>
<td>anti-HIV integrase</td>
<td>seroconversion</td>
<td>detection of anti-p31</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>~70 days</td>
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</table>
Acute HIV Infection and STDs
Pilcher et al. AIDS 18:1-8, 2004

• 1,361 men screened in STD and Dermatology Clinics in Lilongwe Malawi
  • 47% antibody + (chronic HIV Infection)
  • 2.1% (28) with acute HIV (antibody -, RNA +)
    - Inguinal nodes: 11.4% acute HIV
    - Genital ulcer (HSV): 7.8% acute HIV
    - CSW exposure: 9.1% acute HIV

Acute HIV was detected ONLY in symptomatic
STD patients (!!!) implying co-transmission or
“staged” transmission of an STI followed by HIV,
or vice-versa.
Acute HIV Infection and STDs

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Acute HIV was detected ONLY in symptomatic STD patients (!!) implying co-transmission or “staged” transmission of an STI followed by HIV, or vice-versa.
High Prevalence of Acute, undetected HIV infection in a Primary Care Clinic in South Africa

W. Stevens, E. Akkers, M. Myers, T. Motloung, C. Pilcher and F. Venter
Summary of Results

• 12 antibody-negative acute HIV infections missed by HIV antibody ELISA algorithm

1.8% of all HIV infections, 1.0% of all antibody-negative or indeterminate clients

• Prevalence of acute HIV infections in the study population was 0.6% (95% confidence interval: 0.3%, 1.1%)

• Sensitivity of dual-ELISA antibody testing alone for HIV infection was 98.2% (95% confidence interval: 97.0%, 99.1%);
1 Signs and Symptoms

- Fever within a week of ER or clinic visit
- AIDs

One or more of the following:

**SIGNS**
- rash
- lymphadenopathy
- oral/genital/cervical ulcerations
- exudative pharyngitis
- aseptic meningitis
- headache, photophobia, stiff neck

**SYMPTOMS**
- malaise/fatigue
- diarrhea
- weight loss
- night sweats
- anorexia

2 Diagnosing it...

- Identify individuals at risk
- Obtain HIV ELISA test and HIV PCR test*
- If ELISA is negative and PCR is positive, diagnostic criteria have been met.
  *Diagnostic HIV PCR is confirmed, but if unavailable, a "real test" HIV PCR/RT/NA or RNA may be obtained.

3 Positive Diagnosis?

- COUNSEL THE PATIENT
  1. This is a very early HIV infection
  2. Hepatitis may be extremely infectious
  3. If Transmission of HIV is very possible
  4. Sex or drug partner should be notified

- ADVISE THE PATIENT
  1. Significant benefit can result from Early Event Evaluation
  2. Immediately go to your regional Acute HIV Study Center
  3. If there is no Acute HIV Study Center in your area contact your local AEKC listed below for a prompt referral.

Contact your regional
Acute HIV Center

TIMING IS CRITICAL!
Risk factors for HIV

- Race
- Age
- Disabled
- Province
Differential Diagnosis

• Probably chancroid, vaginal discharge of unknown aetiology – will get better
• ?acute HIV
What would I like?

- HIV viral load
- 4\textsuperscript{th} generation HIV, serial ELISA, p24…
- If remains negative, requires good history, examination, non-directed and directed tests
Diagnostic Test Results
Thumbi Ndung’u, BVM, PhD

Associate Professor in HIV/AIDS Research; Director, HIV Pathogenesis Programme (HPP)
Doris Duke Medical Research Institute,
Nelson R. Mandela School of Medicine,
University of KwaZulu-Natal, Durban, South Africa
Discussion of Management

Prof WD Francois Venter, FCP (SA)
Why is Acute HIV Important?

• Viral ‘set point’
• Prevention Opportunity
Dynamics summary

- HIV is not a latent infection
- Replication is rampant
- CD4 $T_{1/2}$ is shortened
- T-cell turnover is very high
- Chronic immune activation
- The virus kills cells, more get made
Where does this depletion occur?

- 80% of all CD4 cells are lost in 1st 17 days!
Background and Rationale

• HIV-1 RNA set point after seroconversion predictive of subsequent disease progression
  – Suggests early events in HIV pathogenesis could influence long-term outcomes
• Symptoms suggestive of rapid disease
• Clinical trials conflicting – benefit, but ?how much – and is it sufficient?
In HIV-1 pathogenesis the die is cast during primary infection

Mireille Centlivre\textsuperscript{a}, Monica Sala\textsuperscript{b}, Simon Wain-Hobson\textsuperscript{b} and Ben Berkhout\textsuperscript{a}

\textit{AIDS} 2007, 21:1–11
Management

• Are there benefits to early ART?
• Transmission risks
Benefits immunologically? Yes…

B cells in early and chronic HIV infection: evaluation of parameters associated with early initiation of antiretroviral therapy

Clinically? Maybe, but ? enough…
## When to Start: 2009 DHHS Guidelines

<table>
<thead>
<tr>
<th>CD4+ Cell Count</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ cell count &lt; 350 cells/mm³</td>
<td>Start ART</td>
</tr>
<tr>
<td>CD4+ cell count 350-500 cells/mm³</td>
<td>Start ART*</td>
</tr>
<tr>
<td>CD4+ cell count &gt; 500 cells/mm³</td>
<td>Panel divided†</td>
</tr>
</tbody>
</table>

### Clinical Conditions Favoring Initiation of Therapy Regardless of CD4+ Cell Count

- History of AIDS-defining illness
- Certain acute opportunistic infections
- Pregnancy
- HIVAN
- HBV coinfection when HBV treatment is indicated
- CD4+ count decline > 100 cells/mm³ per yr
- HIV-1 RNA > 100,000 copies/mL

*Panel divided: 55% strongly recommend and 45% moderately recommend. †50% favor initiating therapy at this stage. 50% view initiating therapy at this stage as optional.
Therapy for Early HIV Infection

Symptomatic (Stages 3 & 4)

Asymptomatic (Stages 1 & 2)

Clinical Symptoms

CD4 Count (cell/mm³)

< 200

200

350

500
But…

- Average age in South African women starting ART is about 32 years, CD4<100…
- Adherence issues, guidelines issues
- Highlights a primary problem: Retention in care
The partner…

• NOT clear he’s the transmitter
• Priority to try to get him in
Sexual transmission of HIV

Cohen MS and Pilcher CD, JID 2005;191:1391-1393

Risk of Transmission Reflects Genital Viral Burden

HIV viral burden in semen

Effect of biological intervention (theoretical)

HIV viral burden in semen
Final reflection

• We can identify HIGHLY infectious HIV patients easily at an STD clinic – but we don’t!

• What would we do with them? Public Health debate re ‘test and treat’

• BUT: finding them IS useful re sexual behaviours
In summary

• Newly diagnosed HIV positive young woman
• Highly likely to get ‘lost to the system’
• Offer INH
• Fertility, condom and transmission advice
• Counsel her partner
Discussion of Epidemiology

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South Africa
Associate Professor of Clinical Epidemiology,
Mailman School of Public Health, Columbia University, New York, USA

Vivek Naranbhai
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