HIV in South Africa: The challenges of a limited formulary

Dr Francois Venter
Reproductive Health and HIV Research Unit
University of the Witwatersrand
September 2009
Talk structure

- Context
- How did we mess up TB?
- Toxicity and resistance
- Other issues
Background…

• South African stats
South Africa: Why is it important? (and why is it different)?

• Size of the country; size of the epidemic; size of ART programme
HIV and South Africa

5 million people
HIV prevalence rates in adults by region, 2007

- Caribbean
- East Asia
- Eastern Europe
- Latin America
- North Africa and Middle East
- Northern America
- Oceania
- South and Southeast Asia
- Sub-Saharan Africa
- Western Europe

Percent infected

World average

Bongaarts J et al, 2008

Global new infections, 2.7 million

<table>
<thead>
<tr>
<th>Country</th>
<th>New Infections</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southern &amp; Eastern Africa</td>
<td>1.5 million (57%)</td>
<td></td>
</tr>
<tr>
<td>Rest of the world</td>
<td>1.2 million (43%)</td>
<td></td>
</tr>
</tbody>
</table>

ESA new infections, Prov. estimate 1.5m

- **Kenya**: 245,162 (16%)
- **Mozambique**: 156,108 (10%)
- **Tanzania**: 139,151 (9%)
- **Uganda**: 78,769 (5%)
- **Eritrea**: 4,838 (1%)
- **South Africa**: 473,499 (31%)
- **Zambia**: 103,077 (7%)
- **Ethiopia**: 94,489 (6%)
- **Angola**: 21,777 (1%)
- **Lesotho**: 22,666 (1%)
- **Malawi**: 86,905 (6%)
- **Zimbabwe**: 45,652 (3%)
- **Rwanda**: 9,225 (1%)
- **Botswana**: 13,518 (1%)
- **Swaziland**: 15,131 (1%)
- **Comoros**: 28
- **Madagascar**: 1,491
- **Mauritius**: 584


- **Era of our Time**: 2007
- **Global new infections**: 2.7 million
- **ESA new infections**: 1.5 million (57%)
- **Rest of the world new infections**: 1.2 million (43%)
The proportion of deaths due to AIDS has shown a staggering increase in the last decade. According to the ASSA2003 Model, in 1995, 3% of deaths were directly due to AIDS. By 2000, this proportion increased to 28%, and by 2005, it reached 46%. The source of this data is the ASSA2003 Model.
Key Indicators of the HIV / AIDS Epidemic in 2006


- KwaZulu-Natal: 40%
- Other: 33%
- Northern Cape: 20%
- Limpopo: 20%
- Western Cape: 17%


- KwaZulu-Natal: 16%
- Western Cape: 5%

Percentage of HIV infected on Treatment in Selected Provinces (2006)

- Western Cape: 8%
- Gauteng: 5%
- Eastern Cape: 3%

- Incidences have peaked in all provinces
- KwaZulu-Natal performs worst on all measures of mortality
  - Accounts for 28.7% of all infections
  - Life expectancy at birth of 43 years
- Incidence rate in the Western Cape is half that of the national average
  - Nearly 1/3 of that of KwaZulu-Natal
- Gauteng accounts for 26.2% of all infections
  - Gauteng only accounts for 17.3% of the infected youth

Source: The Demographic Impact of HIV / AIDS 2006, ASSA
Reality check…

• \( \frac{1}{2} \) all South Africans will contract HIV.
"We will restore science to its rightful place and wield technology's wonders to raise health care's quality..."
“Not only do they give you a beautiful face and skin, but they also protect you from disease.”

— MANTO TSHABALALA-MSIMANG

South African health minister, who advocates garlic and lemon rind as AIDS treatments and warns against anti-retroviral drugs because of dangerous side effects.
New Health Minister: Dr Aaron Motsoaledi
Achievements since 1994…

• Dismantling of the apartheid health system
• Legislative reform (National Health Act, Medical Schemes Act, etc.)
• Adopt District Health System, resulting in establishment of health districts and sub-districts
• Increased access to health services through:
  • The adoption of an essential PHC package of services
  • Removal of user fees for public PHC and all fees (including hospitals) for pregnant women, children under six years of age and people living with disabilities
  • Construction of clinics/ community health centres and revitalisation of hospitals
  • Introduction of community service, scarce skills allowances, Community Health Care Workers and mid-level workers, mainly for the benefit of under-resourced rural areas
• Introduction of strategic programmatic initiatives (HIV/ AIDS, TB, malaria, maternal and child illnesses, lifestyle diseases, etc)
• Private health sector reforms to, *inter alia*, stabilise the medical schemes environment and reduce the costs of drugs for increased access
• “South Africa is a very good laboratory, but a very poor factory” – Jack Koolan
Examples…

• We can do a heart transplant, we can’t do DOTS
• We can run 2010, we can’t run the PSL
• We can look after someone with a CD4 count of 12, we can’t make a clinic full of healthy people work
• Swine flu response, we can’t deal with AIDS
Our health outcomes are bad.....
Results are depressing

**Life expectancy at birth**

- UAE: 76
- India: 69
- EU: 79
- Afghanistan: 44
- Botswana: 51
- Lesotho: 40
- Swaziland: 33
- SA: 45
- Sierra Leone: 35
- Angola: 38

**Maternal Mortality**

- India: 450
- SA: 400
- Iraq: 300
- China: 230
- Namibia: 300
- Brazil: 260
- Chile: 110
- UK: 16
- NL: 16

**Infant Mortality (per 1,000)**

- Botswana: 124
- India: 76
- SA: 69
- Namibia: 61
- China: 27
- Brazil: 20
- Chile: 9
- UK: 6
- NL: 5

Source: Unicef; WHO Maternal Mortality Report, 2007, StatsSA; Monitor Analysis
Results are depressing

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**Maternal Mortality**
- Chile: 31 (2000), 16 (2005)

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38% ‘clearly avoidable
Results are depressing

Needs >R15 billion to fix – Lancet, Aug 2009

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Measurement of Generally Accepted Indicators Reveals that the South African Healthcare System is Functioning Poorly by International Standards

<table>
<thead>
<tr>
<th>Country</th>
<th>2000</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>230</td>
<td>400</td>
</tr>
<tr>
<td>Iraq</td>
<td>250</td>
<td>300</td>
</tr>
<tr>
<td>China</td>
<td>230</td>
<td></td>
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<tr>
<td>Namibia</td>
<td>300</td>
<td>210</td>
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<tr>
<td>Brazil</td>
<td>110</td>
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<tr>
<td>Chile</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>United Kingdom</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Netherlands</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Country</th>
<th>2000</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>1,900</td>
<td>1,800</td>
</tr>
<tr>
<td>India</td>
<td>540</td>
<td>450</td>
</tr>
<tr>
<td>South Africa</td>
<td>230</td>
<td>400</td>
</tr>
<tr>
<td>Iraq</td>
<td>250</td>
<td>300</td>
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<tr>
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<tr>
<td>Brazil</td>
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<tr>
<td>Chile</td>
<td></td>
<td>31</td>
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<tr>
<td>United Kingdom</td>
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<td>13</td>
</tr>
<tr>
<td>Netherlands</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>

Note: MMR = Number of Maternal deaths per 100,000 *Public Sector deliveries estimated. Live births is used as a proxy for the number of pregnancies annually. MMR is an indicator of the quality of a health care system.

South Africa’s war-like death statistics: young women

Female deaths from death notifications 1997-2005
South Africa

- Middle income country: good GDP
Pause...
Health IS underfunded...
Underfunding in Africa:

- 2001, Abuja declaration: 53 governments to put in place policies and legislative frameworks to respond to HIV; re-affirmed in 2005
- Pledged 15 percent of national budgets towards health.
- 2009, only one country (Liberia) has met the target; 67 percent of the countries are yet to hit the 10 percent mark.
Sources: Stats SA and National Treasury
Expenditure trends by function (real 2005/06 prices)

- Education
- Social Development
- Health (national and provincial departments)
- Safety and security
- Roads and transport
- Local government transfers
- Defence
Overall, South Africa getting poor performance relative to cost

Countries sitting above the trend line are producing relatively better performance for the cost per capita inputs that they are investing

Performance vs. Cost Comparison, 2008

Note:  Trend line is a polynomial
Source:  Discovery Health Pool Stream Database, Monitor Analysis
Currently…

- 5 million / total population 45 million – HIV+
- 1 million AIDS
- 300 000 deaths / year (200 000 now on ART)
- ? 70 000 new paediatric infections / year
500,000 need ARV’s EACH year

200,000 well on ARV’s

300,000 dead

200,000 well on ARV’s
How is treatment doing?

• Almost 1 million people on treatment
Proportion of New AIDS Sick Treated per Year and per Province 2005-2007

- New AIDS sick treated in 2005
- New AIDS sick treated in 2006
- New AIDS sick treated in 2007
- New AIDS sick treated in 2008

NSP Target 2011

EC, FS, GP, KZN, LP, MP, NC, NW, WC, RSA
Who did we NOT reach?

Number of Untreated AIDS Cases per Year and per Province

- Untreated AIDS cases 2005
- Untreated AIDS cases 2006
- Untreated AIDS cases 2007

<table>
<thead>
<tr>
<th>Province</th>
<th>Untreated AIDS cases 2005</th>
<th>Untreated AIDS cases 2006</th>
<th>Untreated AIDS cases 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
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<td>WC</td>
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<td>LP</td>
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<td>NW</td>
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<td>FS</td>
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<td>MP</td>
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<tr>
<td>EC</td>
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<td></td>
</tr>
<tr>
<td>GP</td>
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<td></td>
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<tr>
<td>KZN</td>
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</tr>
</tbody>
</table>
ART outcomes - more good news

- National programmes reporting good outcomes

- 1 year survival estimated as 93-95%

- 2 year survival 91%
Outcomes of ART

5 year survival on HAART in Botswana

88.6% (88.1 – 89.2)

Puvimanasinghe JPA et al.
IAC 2008 (MOAB0204)
ART programme – some success

• Life expectancy for males is estimated to have increased to 53.5 in 2009 from 53.3 last year, after dropping every year since 2001

• Infant mortality fell to 46 per 1,000 live births in 2009, compared with 46.4 last year

Stats SA 2009
Limited formulary
TB...

Thanks: Braamie Variava
TB is catastrophic in developing countries, especially sub-Saharan Africa.

Evidence that prior HIV/TB estimates were too low.

1.37 m. estimated incident HIV+ TB cases in 2007.

All % higher in sub-Saharan Africa.
In addition: Highest TB incident and prevalence

- TB-HIV co-infection was approximately 55% in 2002
- The number of people diagnosed with TB trebled between 1996 and 2006 (from 269 to 720 cases of TB per 100,000)
- 900 cases of Extensive Drug Resistant TB were reported between 2004 and 2007

Source: Health Systems Trust reported 722 number; WHO: Global Tuberculosis Control, Surveillance, Planning, Financing reported 940
MDR and XDR?

70% budget

Sputum results not acted on

50% hospital referrals never make it to a TB clinic

Completion rates very poor
MDR and XDR?

“Public health negligence…” Lancet 2006
“You are more likely to get cured from MDR TB in Peru than drug susceptible TB in Johannesburg”

Dr Andrew Black, Pulmonologist, Johannesburg
TB is the ultimate ‘limited formulary’ disease!

• Very old drugs
• MDR drugs less effective, far more toxic, very expensive
• Can we avoid this in HIV?
Toxic!

Failure – VL > 5000

3TC

Efavirenz/ nevirapine

Protease

AZT

ddI

Kaletra

2 Nukes

Non-nuke

Efavirenz/ nevirapine
Potential new guidelines…

• Do NOT address new drugs!
Reasons for switch

Patterns of treatment switches
(2-class regimen only)

Vo et al., JID, Juni 2008
Antiretroviral Efficacy Rates Are Improving in Clinical Practice

- Virologic failure of initial HAART in previously treatment-naive patients from 5 observational cohorts (N = 4143)

## Safety and Tolerability of Select Current Regimens Are Excellent

<table>
<thead>
<tr>
<th>Study</th>
<th>Length</th>
<th>Drug regimen</th>
<th>Discontinuations Due to AEs,* %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI424-089</td>
<td>96 weeks</td>
<td>ATV + d4T + 3TC, ATV/RTV + d4T + 3TC</td>
<td>3, 8</td>
</tr>
<tr>
<td>GS934</td>
<td>48 weeks</td>
<td>EFV + TDF + FTC, EFV + ZDV/3TC</td>
<td>5, 11</td>
</tr>
<tr>
<td>KLEAN</td>
<td>48 weeks</td>
<td>FPV/RTV + ABC/3TC, LPV/RTV + ABC/3TC</td>
<td>12, 10</td>
</tr>
<tr>
<td>ARTEMIS</td>
<td>48 weeks</td>
<td>DRV/RTV + TDF/FTC, LPV/RTV + TDF/FTC</td>
<td>3, 7</td>
</tr>
<tr>
<td>CASTLE</td>
<td>48 weeks</td>
<td>ATV/RTV + TDF/FTC, LPV/RTV + TDF/FTC</td>
<td>2, 3</td>
</tr>
<tr>
<td>HEAT</td>
<td>48 weeks</td>
<td>ABC/3TC + LPV/RTV, TDF/FTC + LPV/RTV</td>
<td>4, 6</td>
</tr>
<tr>
<td>GEMINI</td>
<td>48 weeks</td>
<td>SQV/RTV + TDF/FTC, LPV/RTV + TDF/FTC</td>
<td>4, 7</td>
</tr>
</tbody>
</table>

Estimated Timeline for Availability of New Antiretrovirals

- **PIs**
- **NNRTI**
- **NRTI**
- **Maturation inhibitors**
- **Integrase inhibitors**
- **Entry inhibitors** (anti-gp120, CCR5)

<table>
<thead>
<tr>
<th>Year</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>MK-0518</td>
</tr>
<tr>
<td>2007</td>
<td>Etravirine</td>
</tr>
<tr>
<td>2008</td>
<td>TMC278</td>
</tr>
<tr>
<td>2009</td>
<td>Brecanavir</td>
</tr>
<tr>
<td>2009</td>
<td>Apricitabine</td>
</tr>
<tr>
<td>2009</td>
<td>Vicriviroc</td>
</tr>
<tr>
<td>2010</td>
<td>TNX-355</td>
</tr>
<tr>
<td>2010</td>
<td>GS-9137</td>
</tr>
</tbody>
</table>

- **CXCR4 inhibitors**
- **Integrase inhibitors**
- **Entry inhibitors** (anti-gp120, CCR5)
New ARVs for man with boobs

Alfred Moselakgomo

A Mpumalanga hospital has changed the type of antiretroviral drugs which allegedly made a man develop breasts.

Sowetan reported last week that Sabelo Maepa (not his real name), 42, of Sakhile township in Standerton developed breasts after he took antiretroviral drugs which he said did not suit him.

The biological terms for the man's condition is gynecomastia (development of breasts in men).

A doctor at Standerton Hospital where Maepa was admitted initially said Maepa, who is also on TB medication, was taking a drug called Stavudine when he developed breasts.

Stavudine was approved by the US Food and Drug Administration for adult use in June 1994. It was also approved for pediatric use in 1996, and again as an extended-release version for once-a-day dosing in 2001.

It is the fourth antiretroviral drug on the market and its patent will expire in the US on June 25 next year, according to Aids InfoNet.

Another Standerton hospital doctor, who did not want to be named, said: "Stavudine had an adverse impact on Maepa and he will now be given another drug called Zidovudine."

Zidovudine was the first drug approved for the treatment of HIV. It is a nucleoside analog reverse transcriptase inhibitor, or nucle, according to The Body, a comprehensive website featuring in-depth information on topics ranging from HIV prevention to state-of-the-art treatment issues.

The Body states that these drugs block the reverse transcriptase enzyme. This enzyme changes HIV's genetic material into a form of DNA.

This has to occur before HIV's genetic code gets inserted into an infected cell's own genetic codes.

A source said Standerton Hospital last week referred Maepa back to the wellness clinic in Standerton for examination.

The results of his examination were not immediately available.

"Maepa has been booked for surgery on November 21 at a Johannesburg hospital," he said.

No cost implication has been attached as he is a public patient.

"The cost will be carried by government," he said.

Amphelela Mpho, a health department spokesperson, said he was not aware of any development in Maepa's case.

Case sends shockwaves

Zinlele Mapumulo

Looking for a young and driven candidate?

What people on ARV treatment should know:

- The names of pills
- Your weight
- CD4 Count
- Viral Load
- What they should be cautious about:
  - Losing weight
  - Painful feet
  - Stomach pain or vomiting for over

"Solution is at hand" - doctor

Francois Venter

Sowetan reported a case of a man growing breasts due to the side-effects of antiretroviral treatment.

The story was accompanied by a photograph of the man. It is tragic that the side effects were allowed to become so severe.

This is an occasional side-effect of antiretroviral treatment.

The man in the photograph is the worst case I have seen after many years of using these drugs on my patients.

The side effect usually occurs after several months and very rarely, and patients usually have lots of time to bring this to the attention of their doctors.

It is caused by the redistribution of fat in the body, and can occur in women as well.

He needs to quickly switch his antiretroviral drugs to a different combination which does not cause breast enlargement. The enlargement should slowly recede, but he must keep his doctor alerted, and he may need additional treatments if it does not resolve.

Antiretrovirals, like any drugs, have side-effects, sometimes severe.

But for the vast majority of patients, they are life-saving.

They have changed HIV infection from a death sentence to a manageable chronic disease.

This is not to underestimate the seriousness of what has happened to this man, but to emphasise that though antiretrovirals carry risks, their benefits far outweigh these risks.

In one way this, as well as other serious side-effects, could be reduced, is to replace an antiretroviral called stavudine with one called tenofovir, not currently available in our state treatment programme.

We urge the Department of Health to consider this improvement.

Venter is a specialist doctor in private practice treating HIV patients. See adjacent report.
Who is still taking d4T?

Side effects potentiated by TB Rx

Is there a resistance problem?
CDC Survey: Primary Drug Resistance

<table>
<thead>
<tr>
<th>Resistance to:</th>
<th>1998 (n=257)</th>
<th>1999 (n=239)</th>
<th>2000 (n=299)</th>
<th>2003-2004 (n=787)</th>
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<tbody>
<tr>
<td>Any drug</td>
<td>5.5</td>
<td>8.8</td>
<td>10.7</td>
<td>14.5</td>
</tr>
<tr>
<td>NRTI</td>
<td>5.1</td>
<td>7.1</td>
<td>7.7</td>
<td>7.1</td>
</tr>
<tr>
<td>NNRTI</td>
<td>0.4</td>
<td>2.1</td>
<td>1.7</td>
<td>8.4</td>
</tr>
<tr>
<td>PI</td>
<td>0</td>
<td>0.8</td>
<td>3.0</td>
<td>2.8</td>
</tr>
<tr>
<td>≥2 drug classes</td>
<td>0</td>
<td>1.3</td>
<td>1.3</td>
<td>3.1</td>
</tr>
</tbody>
</table>

For 1998-2000, surveillance included data from 5 cities that participated in all 3 years of the survey. For 2003-2004, surveillance included data from 89 sites in 6 states.

Bennett D, et al. 9th CROI; 2002; Seattle, WA. Abstract 372.
Bennett D, et al. 12th CROI; 2005; Boston, MA. Abstract 674.
New seroconverters:

- Genotyped recent seroconverters (106)
- 6 had NRTI/PI mutations; none NNRTI

Antiretroviral drug susceptibility among drug-naive adults with recent HIV infection in Rakai, Uganda

Susan H. Eshleman a, Oliver Laeyendecker b,c, Neil Parkin d, Wei Huang d, Colombe Chappey d, Agnes C. Paquet d, David Serwadda e, Steven J. Reynolds b,c, Noah Kiwanuka f, Thomas C. Quinn b,c, Ronald Gray g and Maria Wawer g

AIDS, April 2009
Why not in Africa?

- Triple therapy largely the standard of care
- Highly selected patients in most sites
- High levels of care at ART sites
- Reported and measured adherence very high (in state health sites)
Failure after 1st line
Kaplan Meier Estimate of Proportion Remaining on First Line Regimen

Uptake of second-line regimen = 3.3% per annum
1st line failures:

- 96 failures (clinical/immunological),
- Mainly M184V (81%) and NNRTI (93%) mutations; both and at least a single TAM (56%)
- High K65R/K70R rate (23%)
1st line failures:

- Virologically failing:

Wallis et al, in press
## Comparison of all HIVDR studies in SA

<table>
<thead>
<tr>
<th>Site</th>
<th>JHB <em>(Wallis et al)</em></th>
<th>KZN <em>(Marconi et al.)</em></th>
<th>Cape Town <em>(Orrell et al.)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample number Clinic sites</td>
<td>256</td>
<td>115</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>First line regimen</strong></td>
<td>D4T, 3TC, EFV (54%)</td>
<td>D4T, 3TC, EFV (48.7%)</td>
<td>D4T, 3TC, EFV (67%)</td>
</tr>
<tr>
<td></td>
<td>AZT, 3TC, EFV (21%)</td>
<td>AZT, 3TC, EFV (26%)</td>
<td>D4T, 3TC, NVP (15.5%)</td>
</tr>
<tr>
<td>% with failure with resistance</td>
<td>84%</td>
<td>83.5%</td>
<td>85%</td>
</tr>
<tr>
<td>HIV-1 subtype</td>
<td>96.5%</td>
<td>97.4%</td>
<td>97%</td>
</tr>
<tr>
<td>M184V</td>
<td>74%</td>
<td>64.3%</td>
<td>78%</td>
</tr>
<tr>
<td>NNRTI</td>
<td>78%</td>
<td>64.3%</td>
<td>77%</td>
</tr>
<tr>
<td>- K103N</td>
<td>43%</td>
<td>51%</td>
<td>55%</td>
</tr>
<tr>
<td>- V106M</td>
<td>26%</td>
<td>19.1%</td>
<td>31%</td>
</tr>
<tr>
<td>TAMS</td>
<td>33.5%</td>
<td>32.2%</td>
<td>23%</td>
</tr>
<tr>
<td>- TAM-1</td>
<td>8%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>- TAM-2</td>
<td>17%</td>
<td>19.1%</td>
<td></td>
</tr>
<tr>
<td>- Both 1&amp;2 &gt; 3</td>
<td>4%</td>
<td>6.1%</td>
<td></td>
</tr>
<tr>
<td>- Both 1&amp;2 &gt; 3</td>
<td>11%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>K65R</td>
<td>4%</td>
<td>0.3%</td>
<td>9%</td>
</tr>
<tr>
<td>NRTI + NNRTI</td>
<td>68%</td>
<td>64.3%</td>
<td>83%</td>
</tr>
</tbody>
</table>
Summary:

- Resistance will occur, and predictably
- Viral loads seem to protect from TAMS
- Screening in Africa: Community resistance remains low: BUT – unregulated communities, pregnant women, …
Are there consequences to resistance?
Consequences of single-dose nevirapine?

Intrapartum Exposure to Nevirapine and Subsequent Maternal Responses to Nevirapine-Based Antiretroviral Therapy

Gonzague Jourdain, M.D., Nicole Ngo-Giang-Huong, Pharm.D., Ph.D., Sophie Le Coeur, M.D., Ph.D., Chureeratana Bowonwatanuwong, M.D., Pacharee Kantipong, M.D., Pranee Leechanachai, Ph.D., Surabhon Ariyadej, M.D., Prattana Leenasirrimakul, M.D., Scott Hammer, M.D., and Marc Lallemand, M.D., for the Perinatal HIV Prevention Trial Group*
Response to d4T/3TC/NVP in Mothers According to History of Single-Dose Nevirapine

% With Virologic Suppression

Baseline | 3 months | 6 months

VL < 400 c/mL on d4T/3TV/NVP
- No previous NVP: 7% (Baseline), 86% (3 months), 86% (6 months)
- Previous NVP, no detectable mutation: 2% (Baseline), 44% (3 months), 53% (6 months)
- Previous NVP, detectable mutation: 0% (Baseline), 43% (3 months), 34% (6 months)

VL < 50 c/mL on d4T/3TV/NVP
- No previous NVP: 1% (Baseline), 79% (3 months), 75% (6 months)
- Previous NVP, no detectable mutation: 0% (Baseline), 80% (3 months), *68% (6 months)
- Previous NVP, detectable mutation: 0% (Baseline), 80% (3 months), *68% (6 months)

* Significant difference vs group with no previous NVP
Increased Disease Progression With Class-Wide Drug Resistance

Cumulative Survival or Remaining Free of AIDS Events Stratified by Class-Wide Drug Resistance (CWDR)

n=623 patients failed HAART and underwent genotypic testing, then were followed for a median of 19 months (IQR 12-29). Multivariate Cox’s model: increased risk of death was significantly associated with higher HIV RNA, prior AIDS, and detection of 3 CWR (hazard ratio 5.34 [95% CI 1.76-16.24]).

• Cape Town model – if you act on detectable viral loads FAST, >1/2 will suppress!
And:

- Viral intolerance at an all time high – ‘patients who have never been undetectable are becoming so on new drugs’
So.....
Do I want resistance testing as a clinician?

• Absolutely!
• But less toxic drugs? Does it add much?
• Decreasing resistance = lengthening life of drugs/lengthening life of patients
• Resistance does not equal death
• People rarely die on ARV’s, even with resistant virus
• Is it the priority?
“compromise guidelines”

- CD4<350 AND
- Pregnant
- TB
- Sick
- (and PCR pos kids)
- Tenofovir for toxicity, risk, and hep B
- NO provision for 2nd line failure
When Is Antiretroviral Therapy Started?

- Review of data from 2003-2005 from 176 sites in 42 countries (N = 33,008)

High death rate while waiting for ART

Expedited care decreased mortality by 60%

RHRU programme?

- Urban and rural: Initiation CD4 80-100 since 2004
- Johannesburg inner city – average CD4 106, despite 70% coverage, and massive escalation of HIV testing
- ¼ of all South Africans had an HIV test last year (Shisana, HSRC Mandela survey, 2009)
Opportunistic illness

High rates of OI and death above 200 in resource poor settings

ART usually initiated during or immediately after OI

Paeds
CHER STUDY: 76% Reduction in the risk of death with immediate compared to deferred ART

P = 0.0002

Most deaths occurred within first 6 months (i.e., before age 10 months)

<table>
<thead>
<tr>
<th>Time to Death (months)</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 0</td>
<td>Deferred</td>
</tr>
<tr>
<td></td>
<td>125</td>
</tr>
<tr>
<td>Month 3</td>
<td>104</td>
</tr>
<tr>
<td>Month 6</td>
<td>72</td>
</tr>
<tr>
<td>Month 9</td>
<td>44</td>
</tr>
<tr>
<td>Month 12</td>
<td>22</td>
</tr>
</tbody>
</table>
But…

In 2007, only 8% of HIV exposed infants tested in 1\textsuperscript{st} 2 months of life.

### Why CD4 Threshold of <350 for Treatment?
Includes Most Maternal Deaths and Postnatal Infections

**ZEBS Study – L. Kuhn personal communication 2009**

<table>
<thead>
<tr>
<th>CD4 Count</th>
<th>Percent Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500</td>
<td>3.9% 4.5% 1.9%</td>
</tr>
<tr>
<td>350-500</td>
<td>3.5% 2.3% 7.4%</td>
</tr>
<tr>
<td>200-350</td>
<td>7.6% 7.3% 13.3%</td>
</tr>
<tr>
<td>&lt;200</td>
<td>7.6% 15.5% 20.8%</td>
</tr>
</tbody>
</table>

- **84% of maternal deaths**
- **82% of postnatal infections**

**CD4 < 200:** 55% of maternal deaths, 47% of postnatal infections
Which 2\textsuperscript{nd} and 3\textsuperscript{rd} line?
Protease inhibitors

- “Can’t take, won’t take”
- Carole Wallis: 50% of those ‘failing second line’ – no resistance mutations
- PIs expensive, logistically difficult
- BUT: likely to remain the backbone of second line for the next 5 years
- Adherence intervention also important!
Opportunistic illnesses

• Also limited formulary
Cryptococcal meningitis
Mycobacterium avium
CMV retinitis
Associated chronic illnesses

- Lipids, blood pressure, diabetes...
Conclusion

- Existing drugs work and we need to take care of them
- We need to replace d4T
- We need alternative in the
- We need our systems fixed – so that we act on viral loads