Risk Factors for Virologic Failure in a Resource Limited Setting

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ART Need and Coverage

- 34 million people living with HIV
  - 23.5 M (2/3) in SSA
  - 5.6 M (16%) in SA
- 16.7 million people need ART*
  - 11 M in SSA
  - 2.5 M in SA
- 9.7 million people receiving ART
  - 7.5 M in SSA (68%)
  - 2.1 M in SA (84%)

*2010 Guidelines (25.9 M 2013)
UNAIDS 2012
DOH SA 2012
VF and HIV Drug Resistance: No Small Problem

- Worldwide estimates of 3-30% virologic failure within one year of first ART (500K – 5M)*

- 40-95% individuals with > 1 major resistance mutation

- 1.2-25.5% of individuals on ART will have drug resistance within one year (200K – 4.3M)*

- Over time triple class failure will accumulate

* Calculated for 16.7 M requiring ART (15% in SA)

Upward estimate of 645K with at least 1 major resistance mutation in SA if everyone needing ART receives it.
Key Clinical/Programmatic Questions

• Can we predict which patients are likely to experience virologic failure?
  – Before starting
  – While on treatment

• Can we prevent these patients from experiencing virologic failure?
Outline

- Review the Existing Data
- Population-level Early Warning Indicators
- Individual-level Factors for Clinicians
Existing Data
Sinikithemba

- McCord Hospital: founded 1909 in Durban by American missionaries to treat black South Africans; private hospital with public support
- Began caring for HIV/AIDS patients in 1992
- ART available in 2002-3; PEPFAR rollout in 2004 via EGPAF
- Over 6,000 patients on ART
- Active clinical, education and research program, integrated care
- Average rate of VF at 12 mos: 4-8%*

*Recent reports from rural KZN 12-40% (Mutevedzi Bull WHO 2010, CROI 2011) and SA NHLS with 30% overall VL >400
Resistance after First-Line ART

Marconi CID 2008

Percentage of Subjects

≥ 1 signif mutation  Dual Class  Triple Class  NRTI  NNRTI  PI

Marconi CID 2008
## Risk Factors for Drug Resistance (Multivariable Analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>Confidence Interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;35)</td>
<td>3.27</td>
<td>0.92-11.63</td>
<td>0.07</td>
</tr>
<tr>
<td>Recent OI (within 6 months of study enrollment)</td>
<td>2.20</td>
<td>0.70-6.88</td>
<td>0.18</td>
</tr>
<tr>
<td>CD4 count at study enrollment</td>
<td>0.87</td>
<td>0.23-3.33</td>
<td>0.84</td>
</tr>
<tr>
<td>HIV-1 RNA Viral Load at study enrollment &lt;100,000 c/mL</td>
<td>7.97</td>
<td>0.82-77.21</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Marconi *CID* 2008
Virologic Suppression at 6 mo

Percentage of Subjects

<table>
<thead>
<tr>
<th>Category</th>
<th>ITT</th>
<th>AT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>72.6%</td>
<td>86%</td>
</tr>
<tr>
<td>Resistance</td>
<td>86.5%</td>
<td>75%</td>
</tr>
<tr>
<td>No Resistance</td>
<td>75%</td>
<td>45%</td>
</tr>
<tr>
<td>No Genotype</td>
<td>78.3%</td>
<td>87.8%</td>
</tr>
</tbody>
</table>

*/*† Significant

N = 186 120 20 46

Murphy AIDS 2010
Clinical Outcomes at 6 mo

N = 186
Died, clinic default = 5

Percentage of Subjects
Overall
Resistance
No Resistance
No Genotype

LTFU
Died
OI
Hosp

HC Hosp/OI ND
*/† Significant

Murphy AIDS 2010
Risk Factors for Death at 6 mos after Switch NS in MV for VF or Death

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>24-Week Mortality no. (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>141</td>
<td>8 (6)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>71</td>
<td>4 (6)</td>
<td>0.98</td>
</tr>
<tr>
<td>Male</td>
<td>70</td>
<td>4 (6)</td>
<td></td>
</tr>
<tr>
<td>HIV-1 drug resistance at initial ART failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 resistance mutation</td>
<td>122</td>
<td>5 (4)</td>
<td></td>
</tr>
<tr>
<td>No resistance</td>
<td>19</td>
<td>3 (16)</td>
<td>0.04</td>
</tr>
<tr>
<td>Subsequent regimen type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPV/r-based ART</td>
<td>114</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>NNRTI-based ART</td>
<td>20</td>
<td>3 (15)</td>
<td>0.004</td>
</tr>
<tr>
<td>CD4 cell count at initial ART failure (cells/μl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥200</td>
<td>58</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>100-199</td>
<td>52</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>50-99</td>
<td>17</td>
<td>2 (12)</td>
<td></td>
</tr>
<tr>
<td>0-49</td>
<td>12</td>
<td>3 (25)</td>
<td>0.005</td>
</tr>
<tr>
<td>HIV-1 RNA viral load at initial ART failure (copies/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4000-4999</td>
<td>33</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>5000-29,999</td>
<td>50</td>
<td>6 (12)</td>
<td></td>
</tr>
<tr>
<td>30,000-99,999</td>
<td>30</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>≥100,000</td>
<td>27</td>
<td>2 (7)</td>
<td>0.05</td>
</tr>
<tr>
<td>WHO clinical stage at initial ART failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>22</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>25</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>42</td>
<td>4 (10)</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>22</td>
<td>2 (9)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Causes of death were determined in 7 of 8 patients (tuberculosis, N=3; gastroenteritis, N=2; lactic acidosis, N=1, suspected central nervous system mass, N=1, unknown cause, N=1).

1 Seven patients did not initiate a regimen after virologic failure and three patients from this group died.
2 One patient who died did not have a CD4 count at first ART failure.
3 One patient who survived did not have a viral load within 8 weeks of first ART failure.
4 Thirty patients who survived did not have a recorded WHO stage at first ART failure.

Murphy AIDS 2010
Pharmacy refill increases after initiation of 2\textsuperscript{nd} line therapy, then declines; associated with virologic response

Murphy JAIDS 2012
Determinants of ART Response

Toxicity, Adverse Effects, Tolerability, Treatment Fatigue

Access to Potent cART (Properly prescribed Combinations)

Acceptance, Adherence, and Uptake

Behavioral, Socioeconomic, and Cultural Factors

Pharmacokinetics, Absorption, Metabolism, Drug Interactions

Systemic and Intracellular Concentration

Inhibition of Viral Replication

Ongoing Viral Replication

Viral Replication Capacity, Virulence, and Resistance

Host Immune and Intrinsic Factors

Increased Immune Activation, Immunologic Decline, Disease Progression, Increased Transmission, Poor QOL and High Mortality

Decreased Immune Activation, Immune Reconstitution, Arrested Disease Progression, Decreased Transmission, Improved QOL and Survival

Nachega/Marconi IDDT 2011
Socioeconomic, Cultural and Psychological Determinants of Health

Adapted from Munoz 1996

Social Ecological Model
Figure 1: Inclusive Model of Human Behavior. Environment refers to childhood and early adolescent influences on personality development which include the family, education, community, and socioeconomic conditions.
Barriers to Clinical Care

- Poverty/Economic
  - Transportation
  - Food Insecurity
  - Disability Grants
  - Poor social support

- Institutional
  - Long wait times
  - Negative staff experiences
  - Poor health literacy
  - Limited substance abuse treatment and mental health facilities

- Sociocultural
  - Perceived stigmatization
  - Influence of charismatic churches
  - Traditional healers
  - Gender Inequalities

- Political
  - Migration
  - Controversy over provision of HIV Tx
  - Unfavorable policies

Kagee J Health Psycyhol, Global Public Health 2010
Western Cape
• > 50% SA live in poverty (HSRC 2004)
  - 10% living in informal settlements; 40% with extended family; Median household size 4.5 people
  - Income decline associated with VF in Uganda (Alsan CROI 2011)
• >40% food insecurity (Rose Pub Health Nutr 2002)
• Unemployment 25-42% (Kingdon 2004); 80% high school only, 10% middle school; may trade health for disability grant (Ojikutu JID 2007)
• 72% of poor live in rural areas and need to travel long distances to district hospitals (ART rollout sites)

<table>
<thead>
<tr>
<th>Income Decline</th>
<th>1.86 ** (0.45)</th>
<th>1.95 *** (0.47)</th>
<th>1.82 ** (0.49)</th>
<th>1.85 ** (0.50)</th>
<th>1.47 (0.40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Baseline Viral Load</td>
<td>1.20 ** (0.10)</td>
<td>1.20 ** (0.10)</td>
<td>1.20 * (0.11)</td>
<td>1.20 ** (0.11)</td>
<td>1.20 * (0.12*)</td>
</tr>
<tr>
<td>Baseline Asset Index</td>
<td>1.00 (0.06)</td>
<td>0.99 (0.06)</td>
<td>0.98 (0.07)</td>
<td>0.98 (0.07)</td>
<td>1.00 (0.07)</td>
</tr>
<tr>
<td>Depression</td>
<td>1.03** (0.02)</td>
<td>1.02 (0.02)</td>
<td>1.02 (0.02)</td>
<td>1.02 (0.02)</td>
<td>1.02 (0.02)</td>
</tr>
<tr>
<td>Travel Cost</td>
<td></td>
<td></td>
<td></td>
<td>1.07 ** (0.03)</td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.10 *** (0.04)</td>
</tr>
</tbody>
</table>

No. Obs 733 727 523 526 466 464

Logit model of viral rebound adjusted for age, age squared, gender, marital status, literacy, ART start date, CD4 cell count at ART initiation in addition to the covariates listed in the table above. Per cell, RE AOR reported above, standard errors in parentheses below. ***, ** and * indicate significance at the 10, 5 and 1% level respectively.
Institutional

- Vella JAIDS 2010
  - Number of new patients per year
  - Staff training and time commitment
  - Patient to staff ratio (NS)
  - Secure area (early on)
  - Confidentiality


- Dedicated staff, outreach vehicles, contact <30 d after missed visit (Braitstein JIAS 2012)


- Fast Tracking (Geng CROI 2011)

- Adherence clubs (Luque CROI 2012)

*Kredo Cochrane 2013
Sociocultural

• Social marginalization leads to poor retention in care (Goudge SAHARA J 2009)

• Ability to resist stigma and other barriers – impact of Social Capital (Ware PLoS Med 2009, Young HPTN 043 JAIDS 2010, Achieng CROI 2011)
  – negative attitudes/beliefs about PLHIV (feelings of disgust, blame)
  – negative perceptions about PLHIV (discrimination)
  – perceptions of fair treatment for PLHIV (equity)

• Traditional Healers incorporated in ARV programs (Shuster J Comm Health 2009)
Traditional African Medicine

• WHO (2008) est 80% Africans use TAM; 70% Canadians, 42% US use CM
• Babb (2007) 84% of the clinic attendees reported use of traditional medicine at least once for their HIV disease with 32% of them reporting current use; Dahab and Reid (2008) adherence barrier, under-reporting
• Sutherlandia, St. John’s Wort, garlic, and American ginseng have D-D interactions via CYP 450 (Mills 2005, Lee 2006, Izzo 2009)
• Potential toxicities (Hsiao 2003)
• SARCS and RFVF Study (Marconi CID 2008, Murphy AIDS 2010, Sunpath AIDS 2012, Marconi AIDS Pt Care STDs 2013)
  – 70-80% have prior to enrollment at SKT
  – 5-20% have some TAM involvement after ART initiation
  – No relationship to drug resistance, virologic failure or clinical events
• Sutherlandia v. Placebo RCT (Wilson et al.)
  – CD4 > 350, no concomitant ART
  – No impact on CD4 count or VL, no toxicities; currently assessing QOL
• ACTG A5175
Political

- Beliefs about HIV/AIDS
- Controversies over provision of HIV treatment
- Migration (intra- and inter-national)
- “Weak Rights” to the system - access basic services, housing, health services and employment (Balbo 2005)
- Unequal distribution of healthcare expenditure → infrastructural and personnel deficits in public sector
  - Private (20% of popn) > public (80%) spending by 7x per capita (Goudge 1999)
  - Lack of comprehensive and integrated care (Jack JAIDS 2004)
Barriers to Adherence

• Barriers to Care
• Symptoms/QOL
• Psychosocial

Tired of taking ARVs
Fear of taking ARVs in front of others
Difficulty swallowing
Remembering to take pills
Side effects
Cost of meds
Psychosocial

- Number of people in social support network correlated with adherence (Ncama *Int J Nurses Stud* 2008)
- Relationship factors and treatment supporters enhance adherence (Nachega *JAIDS* 2006)
- Intimate Partner Violence/Abuse (Dunkle, Jewkes, Pronyk)
- Depression (Peltzer *BMC Public Health* 2010)
- Dementia (Joska *AIDS Beh* 2010) – 42.4% mild neurocognitive disorder and 25.4% HIV-D in Cape Town starting ART
- Stigma/Disclosure (Lyimo *BMC Pub Health* 2012)
- Alcohol Misuse and a partner with HIV (Naidoo *BMC Public Health* 2013)
Population-Level Early Warning Indicators
Countries Implementing One or More WHO HIVDR Surveys

- Sydney
- Ottawa
- Atlanta
- Tlalpan
- Ponce
- Fort de France
- Rio de Janeiro (2)
- Sao Paolo
- London
- Bordeaux
- Madrid
- Utrecht
- Montpellier
- Dakar
- Abidjan
- Yaounde
- Entebbe
- Kisumu
- Kampala
- Johannesburg (2)
- Moscow
- Shanghai
- Beijing
- Shenyang
- Moscow
- Pune
- Chennai
- Bankok (2)
- Ho-Chi Minh City
- Melbourne
- Sydney
- Jordan

- Laboratories undergoing assessment
- Laboratories accredited by WHO

Jordan CID 2012
• Indicators which speak to concerns about HIVDR

  – Assess factors at individual clinics which are known to create situations favourable to the emergence of HIVDR

  – EWIs provide an alert to clinic and ART programmes -- thus providing an opportunity for corrective action

  – Indicators exist for adults and children

Bennett DE et al., Antivir Ther 2008
## WHO-recommended HIVDR EWIs

<table>
<thead>
<tr>
<th>EWI</th>
<th>EWI Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prescribing practices</td>
<td>100%</td>
</tr>
<tr>
<td>2. Lost to follow-up at 12 months</td>
<td>≤ 20%</td>
</tr>
<tr>
<td>3. Retention on first-line ART at 12 months</td>
<td>≥ 70%</td>
</tr>
<tr>
<td>4. On-time drug pick up</td>
<td>≥ 90%</td>
</tr>
<tr>
<td>5. On-time appointment keeping</td>
<td>≥ 80%</td>
</tr>
<tr>
<td>6. Drug supply continuity</td>
<td>100%</td>
</tr>
<tr>
<td>8. Viral load &lt;1000 copies/ml at 12 months</td>
<td>≥ 70%</td>
</tr>
</tbody>
</table>

Bennett DE et al., *Antivir Ther* 2008
Collated results provide a **national level** At-a-glance assessment of site performance

**National Level Reporting**

<table>
<thead>
<tr>
<th>Site</th>
<th>EWI 1: On-time Pill Pick-up</th>
<th>EWI 2: Retention in Care</th>
<th>EWI 3: Pharmacy Stock-outs</th>
<th>EWI 4: Dispensing Practices</th>
<th>EWI 5: Virological Suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95%</td>
<td>75%</td>
<td>100%</td>
<td>70%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>70%</td>
<td>50%</td>
<td>100%</td>
<td>15%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>100%</td>
<td>75%</td>
<td>75%</td>
<td>0%</td>
<td>95%</td>
</tr>
<tr>
<td>4</td>
<td>85%</td>
<td>-</td>
<td>100%</td>
<td>0%</td>
<td>78%</td>
</tr>
<tr>
<td>5</td>
<td>98%</td>
<td>95%</td>
<td>0%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Countries reporting on the use of WHO HIVDR Early Warning Indicators

As of 2011, 124 rounds of EWI monitoring in 58 countries in > 2000 clinics
ART Program Use of EWI Results

1. Strengthened record keeping systems
   • Formation of clinic specific care optimizing committees\(^1\)
   • Validation of existing electronic record keeping systems\(^1,2,3\)
   • Adjustments in pharmacy record keeping to permit on time pill pick up assessments\(^3\)
   • Pilot of enhanced defaulter tracing to identify patients missing drug pick-ups with the goal of reengaging in care within 48 hours\(^1\)
   • General strengthening of records\(^4,5,6,7,8\)

2. Seek funding support from partners to scale-up EWI\(^9\)

3. District teams to support adherence and trace patients LTFU\(^1,10,11\)

4. Scale-up viral load testing\(^5\)

5. Regular review of patient pill pick-up and establishment of formal referral system to document transfers-in/out\(^6\)

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\(^1\)Hong et al. *JAIDS* 2010; 2 Anna Jonas, MoHSS Namibia, personal communication; \(^3\)Dawn Pereko, MSH Namibia, personal communication; \(^4\)Jack N et al. *CID* (in press); \(^5\)Ye M et al. *CID* (in press); \(^6\)Daonie e et al. *CID* (in press); \(^7\)Nhan DT el al. *CID* (in press); Hedt BL et al., *Anti Viral Ther* 2008; \(^8\)Paula Mundari, Uganda National ART Programme, IAS 2010, Vienna; \(^10\)Evelyne B, National ART Program, Burundi, personal communication; \(^11\)Anna Jonas, MoHSS Namibia, personal communication.
HIVDR Early Warning Indicators (EWI)

- Programmatic Level*
  - Prescribing practices
  - LTFU 12 mos ART
  - Retention on 1st Line ART at 12 mos/VL UD
  - Timely ARV pickup
  - ARV appointments
  - ARV shortages
  - Adherence
  - Baseline HIVDR

- Individual Level
  - Pharmacy Refill Data/Clinic Visits
  - Pill Counts/Self-Reported Adherence
  - Clinical Risk Factors
  - Baseline Minority Drug Resistance
  - Psychosocial Risk Factors

*WHO recommends (http://www.who.int/hiv/topics/drugresistance/indicators/en/index.html)
Risk Factors for Virologic Failure Study
Questions

• Who  – is at risk?
• What  – are the barriers?
• Why   – do these barriers exist?
• How   – can we reduce the risk?
Methods

- Patients had to be $\geq 18$ yo and on $\geq 5$ months of their first ART regimen (substitutions allowed for toxicity)
- Unmatched case-control study
  - 158 Cases: VL $> 1000$ cpm
  - 300 Controls: (2:1) virologic suppression (VL $\leq 1000$ cpm)
- McCord Hospital
- Eligible patients were enrolled between October 2010 and June 2012
Methods

• Data Collection:
  – Semi-structured interview in preferred language, coordinator blinded to case/control status
    • Questionnaire – demographic, socioeconomic (including a wealth index, employment, education and cohabitants), psychological (including substance abuse, food insecurity, traditional medicine use, safe sex practices, faith, stigma and intimate partner violence), modified ACTG adherence questionnaire, and clinic satisfaction indices
    • Kessler 10
    • Neurocognitive assessment and Pill count
  – Study physician history/physical
    • Symptom screen
    • Karnofsky score
    • Clinical information, pharmacy refills and laboratory data from the chart
Methods

• Statistical Analysis:
  – Access was calculated using the medication possession ratio (MPR)
  – Adherence was calculated using unannounced pill counts and expected pill count from the pharm refills
  – Multivariate model selection was performed by domain; significant variables were carried over to final models
    • Model 1 – Baseline variables
    • Model 2 – Complete model without Adherence or Access
    • Model 3 – Complete model with Adherence and Access
# Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (300)</th>
<th>Case (158)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment (mean)</td>
<td>40.9</td>
<td>37.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (%female)</td>
<td>71.0</td>
<td>52.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Tuberculosis (%yes)</td>
<td>54.7</td>
<td>55.1</td>
<td>1.00</td>
</tr>
<tr>
<td>Lipodystrophy (%yes)</td>
<td>37.0</td>
<td>15.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recent CD4 count in cells/µL (median)</td>
<td>359.0</td>
<td>206.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recent CD4 count (%&gt;350 cells/µL)</td>
<td>52.0</td>
<td>22.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean ART Duration (months)</td>
<td>33.0</td>
<td>24.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current ART regimen contains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>17.3</td>
<td>27.8</td>
<td>0.0077</td>
</tr>
<tr>
<td>Zidovudine (ZDV)</td>
<td>24.7</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td>Other (tenofovir, didanosine, abacavir)</td>
<td>58.0</td>
<td>57.0</td>
<td></td>
</tr>
<tr>
<td>Fluconazole use in the past 6 months (%yes)</td>
<td>1.0</td>
<td>8.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TS use in the past 6 months (%yes)</td>
<td>44.7</td>
<td>63.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>INH or RIF use in the past 6 months (%yes)</td>
<td>9.3</td>
<td>21.5</td>
<td>0.0005</td>
</tr>
<tr>
<td>ETB use in the past 6 months (%yes)</td>
<td>1.3</td>
<td>5.7</td>
<td>0.014</td>
</tr>
</tbody>
</table>

*Marconi AIDS Pt Care STDs*
Employment Status

80% report having some source of income
30% receive some income from family members
Median number of individuals supported by patient’s income: 3.5
Symptoms in the past 4 weeks

- 10% Feel symptoms are ARV related
- 20% Feel symptoms are a barrier to taking ARVs
Probability of VF by Access or Adherence

Marconi AIDS Pt Care STDs
Correlation between Access and Adherence variables for cases and controls

\[ \rho = 0.68 ; p < 0.0001 \]
<table>
<thead>
<tr>
<th>Domain/Risk Factor</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per 5 year increase)</td>
<td>0.956**</td>
<td>0.837†</td>
<td>0.860</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.995**</td>
<td>2.262**</td>
<td>2.418**</td>
</tr>
<tr>
<td><strong>Socioeconomic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education (per 1 year)</td>
<td>1.771†</td>
<td>1.112</td>
<td>1.108</td>
</tr>
<tr>
<td>Transportation (personal)</td>
<td>1.789</td>
<td>2.034</td>
<td></td>
</tr>
<tr>
<td>Pay for care (family/spouse)</td>
<td>1.517</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychosocial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faith activity (none)</td>
<td>1.634*</td>
<td>1.722†</td>
<td>1.862*</td>
</tr>
<tr>
<td>Practice safe sex (&lt;always)</td>
<td>---</td>
<td>0.600***</td>
<td>0.623**</td>
</tr>
<tr>
<td>Family HIV+ (none)</td>
<td>0.690*</td>
<td>0.593†</td>
<td>0.860*</td>
</tr>
<tr>
<td>Treatment supporter (yes)</td>
<td>1.991*</td>
<td>1.910</td>
<td>1.783</td>
</tr>
<tr>
<td>Clinic feel pleased (yes)</td>
<td>---</td>
<td>0.446*</td>
<td>0.509*</td>
</tr>
<tr>
<td>Depression (12+)</td>
<td>---</td>
<td>3.136***</td>
<td>3.021**</td>
</tr>
<tr>
<td><strong>Symptoms and Exam</strong></td>
<td>---</td>
<td>2.532**</td>
<td>2.470**</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.555*</td>
<td></td>
<td>2.079</td>
</tr>
<tr>
<td>Sadness</td>
<td></td>
<td></td>
<td>1.409</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>1.720†</td>
<td></td>
<td>1.992*</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipodystrophy (yes)</td>
<td>---</td>
<td>0.429*</td>
<td>0.608</td>
</tr>
<tr>
<td>Log CD4 (per 1.0 increase)</td>
<td>---</td>
<td>0.079***</td>
<td>0.079***</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARV duration (per 1 month)</td>
<td>0.995</td>
<td>1.001</td>
<td>1.008</td>
</tr>
<tr>
<td>Recommend HIV clinic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friend vs Family</td>
<td>0.424*</td>
<td>0.311*</td>
<td>0.266*</td>
</tr>
<tr>
<td>Other vs Family</td>
<td>0.446*</td>
<td>0.376*</td>
<td>0.397*</td>
</tr>
<tr>
<td>Provider vs Family</td>
<td>0.879*</td>
<td>0.760*</td>
<td>0.855*</td>
</tr>
<tr>
<td>First Clinic (SKT)</td>
<td>0.503†</td>
<td>0.440†</td>
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</tr>
<tr>
<td>ARV training sessions (3+)</td>
<td>0.350†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence counseling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4 vs 0-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5+ vs 0-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZDV vs d4T</td>
<td>0.619*</td>
<td>0.649†</td>
<td>0.691†</td>
</tr>
<tr>
<td>Other vs d4T</td>
<td>0.489*</td>
<td>0.455†</td>
<td>0.435†</td>
</tr>
<tr>
<td>Recall ARVs (TV/radio)</td>
<td>---</td>
<td>3.519**</td>
<td>3.681**</td>
</tr>
<tr>
<td>Trimethoprim/Sulfa (yes)</td>
<td>1.625†</td>
<td>0.624</td>
<td></td>
</tr>
<tr>
<td>Fluconazole (yes)</td>
<td>4.973*</td>
<td>2.636</td>
<td>3.006</td>
</tr>
<tr>
<td>Ethambutol (yes)</td>
<td>2.729</td>
<td>2.800</td>
<td>3.025</td>
</tr>
<tr>
<td><strong>Access (0.1)</strong></td>
<td>---</td>
<td>---</td>
<td>0.763*</td>
</tr>
<tr>
<td><strong>Adherence (0.1)</strong></td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>
ROC Curves for Each MV Model

Marconi AIDS Pt Care STDs

AUC = 0.8881
AUC = 0.7824
AUC = 0.8867

ROC Curve for Selected Model
Area Under the Curve = 0.7824

ROC Curve for Selected Model
Area Under the Curve = 0.8867

ROC Curve for Selected Model
Area Under the Curve = 0.8881

Marconi AIDS Pt Care STDs
Conclusions

• Low CD4 count, younger age and male gender were associated with VF, confirming findings from previous studies.

• Although economic/structural barriers were associated with VF, none of these factors remained in the final models.

• Psychological factors had the greatest universal impact including depression and fatigue, having no active faith, the clinic experience, family members with HIV, and who recommended the patient for treatment.

• Unsafe sex is likely a marker of risky behavior.

• The use of d4T was associated with VF when compared to ZDV, TDF, ABC and ddl.

• The models were all robust and could be used in this setting to identify individuals with baseline and on-treatment risks thereby enabling targeted approaches for adherence interventions.

• The models could also be a useful adjunctive measure if viral loads are not available.
<table>
<thead>
<tr>
<th>Baseline (While Initiating or Suppressed on ART)</th>
<th>On ART Without Access/Adherence Measures*</th>
<th>On ART With Access/Adherence Measures*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Depression</td>
<td>Depression</td>
</tr>
<tr>
<td>Gender</td>
<td>Unsafe sex practices</td>
<td>Unsafe sex practices</td>
</tr>
<tr>
<td>Faith</td>
<td>Clinic Experience</td>
<td>Clinic Experience</td>
</tr>
<tr>
<td>Family Member HIV+</td>
<td>Fatigue</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Treatment Supporter</td>
<td>Diarrhea</td>
<td>Rash</td>
</tr>
<tr>
<td>Clinic Recommendation</td>
<td>Lipodystrophy</td>
<td>Current CD4 count</td>
</tr>
<tr>
<td>Current Regimen</td>
<td>Current CD4 count</td>
<td>ARV Reminders</td>
</tr>
<tr>
<td>Fluconazole Use</td>
<td>ARV Reminders</td>
<td>Adherence</td>
</tr>
</tbody>
</table>

*These factors do not include those that were identified as baseline risk factors.

Marconi  *AIDS Pt Care STDs*
- "The lines are too long"
- "I miss appointments because the clinic is too far to travel"
- "My pastor says I should not take ARVs"
- "I do not take my pills if I have to take it in front of others"
- "I feel too tired to go to the clinic"
- "I miss appointments because the clinic is crowded"
- "I do not like to take my pills as they make me feel sick"
- "I forget to take my pills"
Summary

- Consider all aspects of the treatment paradigm with a key focus on adherence
- Pharmacy refills and pill counts are inadequate alone to predict failure
- Programs can ask a limited set of questions at initiation and follow-up to identify patients' risk (or have VF if limiting testing) as well as enable targeted interventions
- Important to focus on both structural (institutional and economic) as well as psychosocial factors when designing interventions for patients
- Need to validate model in other settings (rural and peri-urban)
- Using individual-level EWI, interventions can be tailored

**Virologic failure is an emergency w/ or w/o resistance**
Acknowledgments

**McCord Hospital**
- Sabelo Dladla
- Jane Hampton
- Helga Holst
- Sally John
- Roma Maharaj
- Phacia Ngubane
- Claudia Ordonez
- Melisha Pertab
- Sifiso Shange
- Henry Sunpath

**UKZN/DDMRI/RKK/Bethesda**
- Jaysingh Brijkumar
- Kelly Gate
- Michelle Gordon
- Yunus Moosa

**Support**
- NIH/NIAID 1R01AI098558-01A1
- Emory University CFAR
- Harvard University CFAR
- Bayer Diagnostics
- Gilead Pharmaceuticals

**Emory University**
- Hannah Appelbaum
- Carlos del Rio
- Anna Hare
- Monique Hennink
- Brent Johnson
- Rachel Kearns
- David Stephens
- Baohua Wu
- Peng Wu

**Harvard/Einstein/MSF/JHU**
- Daniel Kuritzkes
- Zhigang Lu
- Richard Murphy
- Jean Nachega
Special Thanks to the staff and patients of Sinikithemba and iThemba Clinics…

…and my family for forbearance.