

Validating Definitions of Antiretroviral Treatment Failure in Malawi

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Background

- **The Malawi ART program scale-up:
>100,000 patients started on first line treatment**
- **ART failure is inevitable in large numbers of patients**
- **Demand for second line ART will be high**

Second line ART (AZT/3TC/TDF/Lopinavir/r)

1. More Complicated

- Drug (TB) and food Interactions**
- Requires lab monitoring**
- Higher pill burden**

2. Expensive

- \$150/month vs. \$13/month**

3. Side effects

Background

- **ART Failure Definitions**
 - **Virological**
 - HIV-RNA detectable
 - **Immunological**
 - Decline in CD4 count
 - **Clinical**
 - New clinical events suggestive of disease progression

Treatment Failure Timeline



Criteria used in Malawi:

Clinical (mainly) and Immunological

Background

- **It is critical to determine the best definition of ART failure:**
 - **Avoid unnecessary switch to second line ART**
 - **Avoid switching too late**
 - **Increasing drug resistance**
 - **compromises response to second line ART**
 - **Severe clinical events**

Methods

Prospective study of patients meeting the Malawi ART guidelines criteria for ART failure

- Validate ART failure definitions
- Follow patients on second line ART

Methods

- **Two-center study:**
 - **Lighthouse/UNC Project**
 - **Lilongwe (Central Region)**
 - **ART clinic of Queen Elizabeth Central Hospital**
 - **Blantyre (Southern Region)**

Methods

- **Clinical ART failure**
 - New WHO Stage IV condition
 - OR
 - Progressive/Worsening WHO Stage IV condition
- **Immunological ART failure**
 - > 30% Decline from peak or below pre-treatment value
- **Clinical and Immunological Definitions were validated with HIV-RNA**
 - VL < 400 = rejected
 - VL > 400 = confirmed: true ART failures

Methods

- **Greater than 6 months on Treatment**
- **Adherent to First Line Regimen**
- **Analysis from Dec 2005 to Jan 2007**

Results

152 patients identified as ART Failure Suspects

Malawi ART Guidelines Definitions

- 114 (75%) Immunological**
- 32 (21%) Clinical**
- 6 (4 %) Both Clinical and Immunological**

Features of ART Failure suspects

Characteristic	Mean (range)
Age	39 years (13-67)
Gender	51% Female
CD4	182 (1-927)
Duration on ART	33 months (7-120)

Confirmed ART failures

- 90 / 152 (59%) of Failure suspects were confirmed==**Had Detectable HIVRNA**
 - Clinical 68%
 - Immunological 58%

Clinical Conditions

Stage 4 Condition	N	% Confirmed Failures >400 copies/ml
KS	9	31%
EPTB	8	75%
Wasting	8	75%
Esophageal Candidiasis	7	100%
Cryptococcal Meningitis	2	0%

Analysis

Characteristic	Virologic Failures N=90	Non-Failures N=62	P-value
Age (years)	37.5	41.5	0.03
Female gender	51%	52%	0.95
Duration on ART	40 months	25 months	<0.0001
CD4 count	162 cells	212 cells	0.08

Risk Factors for Confirmed Virologic Failure: HIVRNA>400 copies

Characteristic	Odds Ratio [95% CI]
Sex (Male)	0.61 [0.24 - 1.55]
Age < 18 years	6.45 [0.66 – 62.8]
ART > 3 years	8.80 [2.9 - 26.7]
CD4 <200	3.00 [1.2 - 7.8]
Active Tuberculosis	0.70 [0.21 – 2.34]
Wasting	1.04 [0.15 – 0.71]
Kaposi Sarcoma	0.28 [0.07-0.90]

Misclassification of ART failure

- **KS +/- Chemotherapy**
 - Lowers CD4 count to suggest failure
- **KS Disease Progression**
 - KS progresses despite virological suppression
 - **Excluding KS from the analysis**
 - Clinical Failure 75% correct
 - Immunologic Failure 66% correct

Limitations

- Small sample size, particularly for clinical definitions
- Routine Viral load testing not done at either clinical setting
 - True Sensitivity/Specificity can't be determined
- “Routine” 6 monthly CD4 testing only done at Lighthouse
 - Baseline CD4 often not available on referral cases

Recommendations

- 1. Viral Load testing should be used to confirm ART failure prior to switching to second line treatment**
- 2. Immunological ART failure definitions are particularly vulnerable to misclassification**
- 3. Combinations of clinical criteria, duration on ART and CD4 could be explored as ART failure definitions**

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