Viral suppression versus immunologic criteria for antiretroviral treatment failure

Evaluated by APIN Plus in Nigeria

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Background

- Viral load monitoring is generally accepted as being significantly more sensitive for detecting early ARV failure, it is not widely available in resource limited settings

- In absence of VL monitoring, WHO (2006) guidelines provide clinical, CD4, and virologic definitions of treatment failure for patients on 1st line ART

Clinical failure [a]	New or recurrent WHO stage 4 condition [b c]
CD4 cell failure [d]	• Fall of CD4 count to pre-therapy baseline (or below); or • 50% fall from the on-treatment peak value (if known); or • persistent CD4 levels below 100 cells/mm^3 [e]
Virological failure	Plasma viral load above10 000 copies/ml [f]

www.who.int/hiv/pub/guidelines/adult/en/

Harvard PEPFAR in Nigeria

- Since 2004, the APIN+/ Harvard PEPFAR Program has provided HIV care and treatment to over 85,000 adults
- Patients undergo baseline CD4 and VL testing, with repeat testing 3 and 6 months after ART initiation, then every 6 months thereafter
- WHO defined CD4 criteria for immunologic failure:
  - Fall of CD4 count to pre-therapy baseline (or below); or
  - 50% fall from the on-treatment peak value (if known); or
  - Persistent CD4 levels below 100 cells/mm^3
- Virologic failure is defined as 2 consecutive VL measurements $\geq$1,000 copies/mL after 6 month on ART.
  - Considered the gold standard in this comparative study.

Results

- 9,690 individuals met the following criteria and were included in this analysis :
  - ART-naïve at baseline
  - Available CD4 and VL measurements at baseline and after 6 months on ART.
  - Excluded if both CD4 and VL were not available at or after failure.

Results

- **Using virologic monitoring as the gold standard (n=9,690), and excluding cases of failure with concurrent TB infection:**

	VIR Failure	Vir NOT Failure	*Row Total*
IMM Failure	1355	1712	3067
IMM NOT Failure	1158	5465	6623
Column Total	2513	7177	**9690**

  - **Sensitivity: 53.9%**
  - **Specificity: 76.1%**
  - **PPV: 44.2%**
  - **NPV: 82.5%**

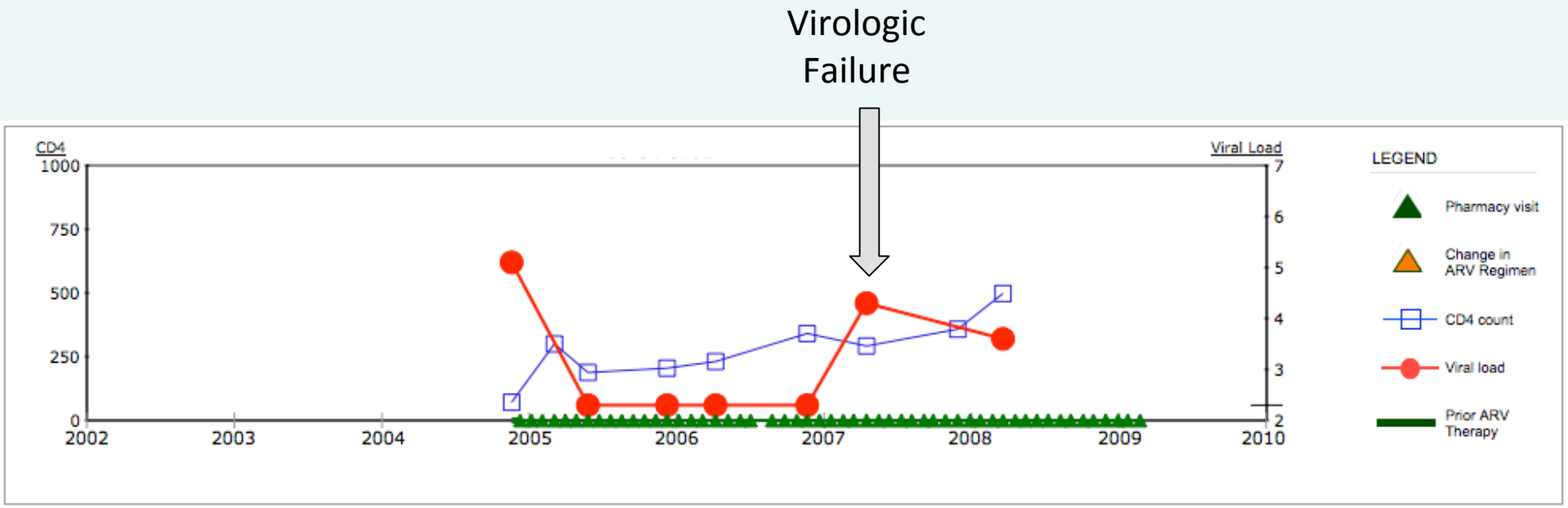
Compared to gold standard of virologic failure, immunologic criteria had low sensitivity for detecting ARV failure.

Virologic failure *without* Immunologic failure

	VIR Failure	Vir NOT Failure	*Row Total*
IMM Failure	1355	1712	3067
IMM NOT Failure	1158	5465	6623
Column Total	2513	7177	**9690**

- **Immunologic criteria had low sensitivity (53.9%) for true virologic failure**
  - Not only would patients be switched unnecessarily, but a substantial number of virologic failures would also have been missed
- Mean time to failure for patients with virologic failure, but without immunologic failure was 14.6 months (n=1158):

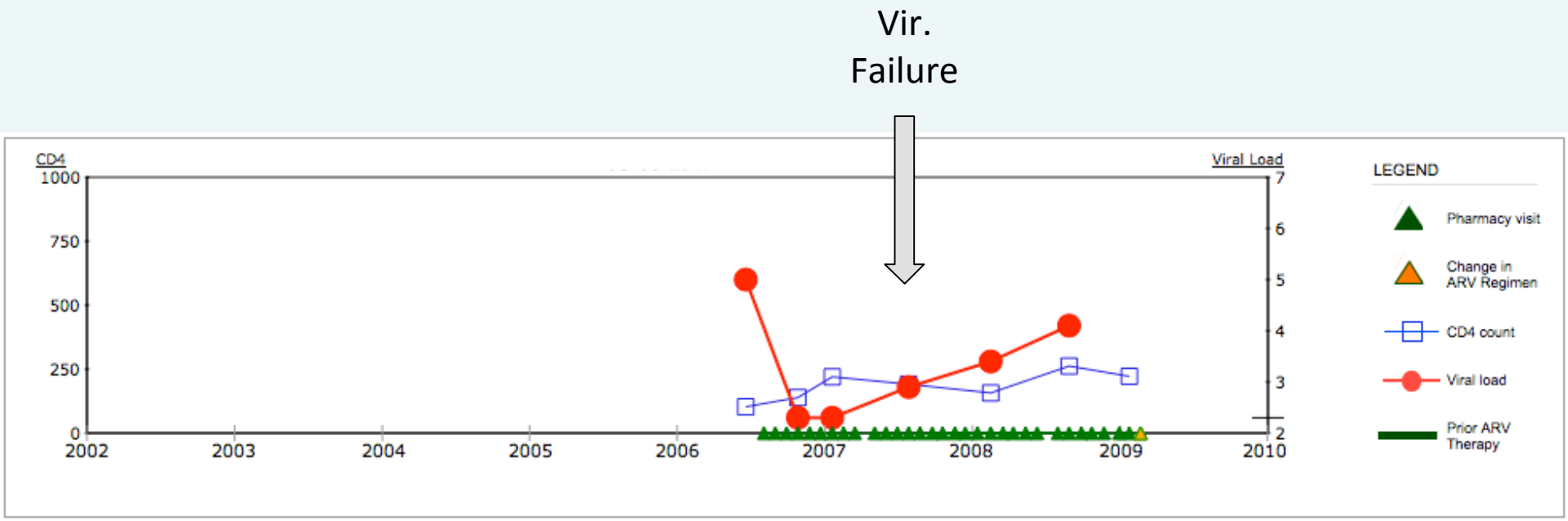
Virologic failure in the absence of immunologic failure



- **Poor sensitivity (53.9%) of CD4 criteria to detect true virologic failure**

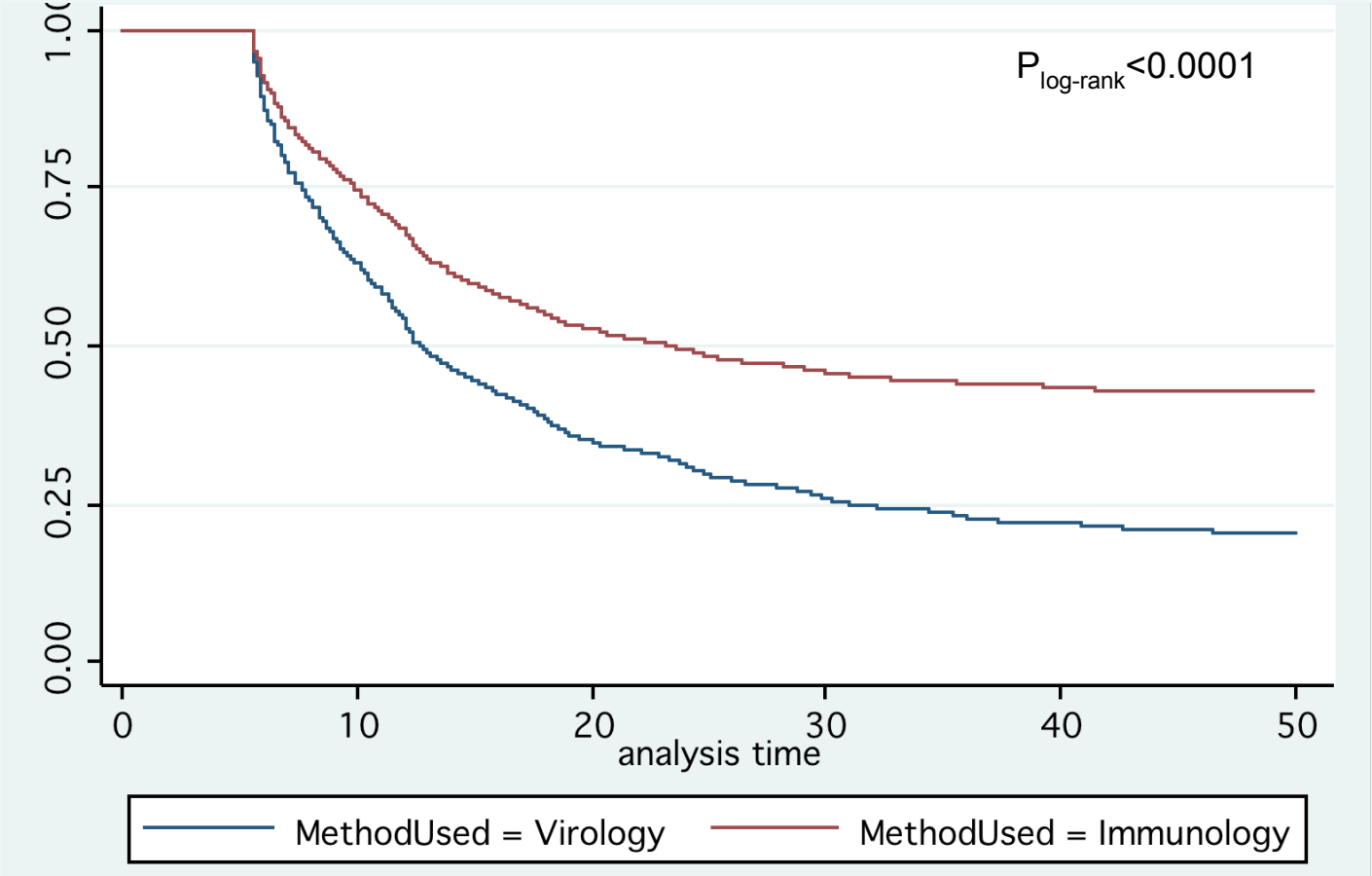
Virologic failure in the absence of immunologic failure

High false negative rate (1158/2513; 46.1%) when CD4 criteria used to detect virologic failure



Comparison of time to failure rates in those detected by virology vs immunology

This dataset includes all patients who failed (by virology and/or immunology)



Immunologic failure *without* virologic failure

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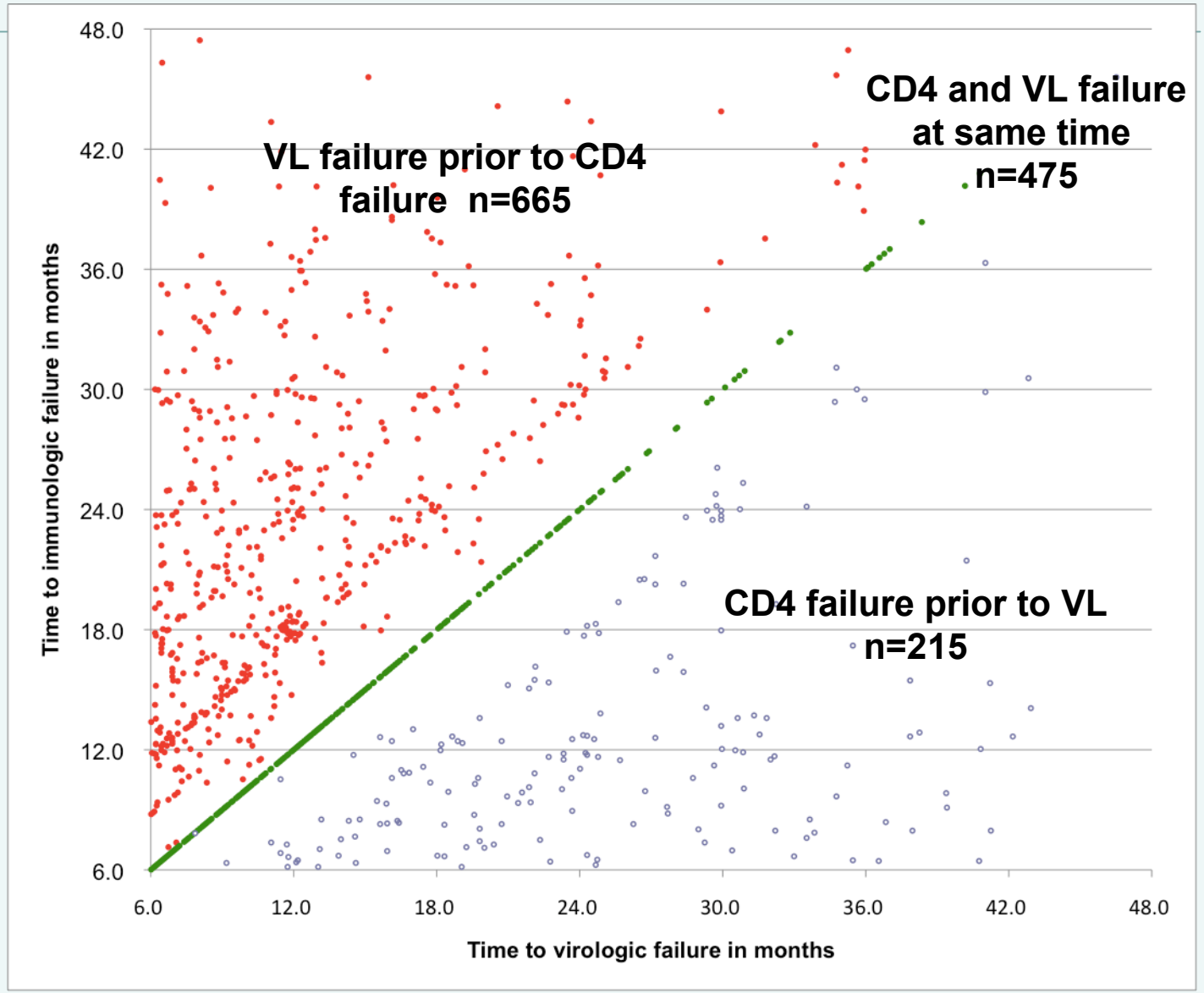
- Low PPV (44.2%) suggests that nearly half of patients identified as failing by CD4 criteria are not actually failing
  - This would result in high rates of unnecessary switches to costly second-line regimens
- Low specificity (76.1%) suggests that 23.9% are falsely identified as failing despite suppressed viral load
- Mean time to failure for patients with immunologic failure without virologic failure **17.5** months

Time to Failure with both Virologic and Immunologic Failure (n=1355)



Model for Assessing Costs

- If we assume:
  - v = $ per month to measure CD4 + VL
  - c = $ per month to measure CD4 only
  - t = time to 1st-line failure, requiring switch to 2nd-line
  - T = time to end of study and/or death
  - x = $ per month for 1st-line therapy (approximately $120 per pt/year)
  - w = $ per month for 2nd-line therapy (approximately $700 per pt/year)

- Total Costs (TC_v) of CD4 + VL monitoring:
  - $TC_v = Tv + xt + w(T-t)$
- Total costs (TC_c) of CD4 monitoring alone:
  - $TC_c = Tc + xt' + w(T-t')$

Basic Cost Analysis

- Number of people who would have been switched to 2nd-line therapy based on 2 methods:
  - CD4 + VL: 2513
  - CD4 alone: 3067
  - 22% increase in 2nd-line switches

- For the 9690 patients in this study cohort, the cost of care over a median study follow-up of 33 months is:

  - Total Costs (TC_v) of CD4 + VL monitoring:
    - $TC_v = Tv + xt + w(T-t)$ = **$6,960,456**
  - Total costs (TC_c) of CD4 monitoring alone:
    - $TC_c = Tc + xt' + w(T-t')$ = **$6,543,905**

- **6.4%** increase in costs of care associated with VL monitoring

Limitations

- Factors which **minimize** costs of VL monitoring:
  - Patients with failure not detected by CD4 monitoring alone, may have increased costs associated with subsequent OIs that occur because failure was not identified early
  - The “cost” associated with accumulated resistance in patients maintained on failing ART regimens needs to be considered
  - Costs are low estimates since 2nd line therapy costs included for 33 months rather than lifetime
- Factors which **increase** cost of VL monitoring:
  - Start-up costs of both VL and CD4 monitoring capabilities needs to be considered.
- Further analyses taking into account cost of new OIs, accumulated ART resistance and scale-up costs are underway

Immunologic vs Virologic Failure

Country	Sample size Follow-up	Sensitivity	Specificity	
South Africa Mee at al. AIDS 2008	N=324 12 mo.	21.2%	95.8%	
Uganda Reynolds et al. AIDS 2009	N=1133 10.2 mo.	23%	90%	
Nigeria Kanki et al	N=9690 33 mo.	53.9%	76.1%	WHO - 3 immunologic criteria

Targeted Viral load Testing

Country	Sample size Follow-up	Sensitivity	Specificity	Predictors
Cambodia Lynen et al, AIDS 2009	N=764 12 mo.	41.9%	92.6%	CD4, Hb, pruritic eruption, visual analog scale
Uganda Meya et al, JIAS 2009	N=496 13 mo.	67% (31%) WHO	82% (87%) WHO	CD4, adherence

Summary

- This is the largest study to date comparing the ability of WHO Immunologic criteria to predict viral failure
- CD4 criteria are insensitive in detecting virologic failure
- CD4 criteria have a low specificity and PPV such that patients are misclassified as failures despite virologic suppression
  - Could result in switch to more expensive, less convenient regimen
- VL monitoring appears to add minimal incremental cost (6.4%) while avoiding misclassification of failures and missed opportunities for earlier switching
- Development of cost –effective VL technologies should be encouraged