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Failure of immunologic criteria to appropriately identify antiretroviral treatment failure in Uganda

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Abstract

Objective—Most antiretroviral treatment program in resource-limited settings use immunologic or clinical monitoring to measure response to therapy and to decide when to change to a second line regimen. Our objective was to evaluate immunologic failure criteria against gold standard virologic monitoring.

Design—Observation cohort

Methods—Participants enrolled in an antiretroviral treatment program in rural Uganda who had at least 6 months of follow-up were included in this analysis. Immunologic monitoring was performed by CD4 cell counts every 3 months during the first year, and every 6 months thereafter. HIV-1 viral loads were performed every 6 months.

Results—1133 participants enrolled in the Rakai Health Sciences Program antiretroviral treatment program between June 2004 and September 2007 were followed for up to 44.4 months (median follow-up 20.2 months; IQR 12.4–29.5 months). WHO immunologic failure criteria were reached by 125 (11.0%) participants. A virologic failure endpoint defined as HIV-1 viral load (VL) >400 copies/ml on two measurements was reached by 112 participants (9.9%). Only 26 participants (2.3%) experienced both an immunologic and virologic failure endpoint (2 VL>400 copies/ml) during follow-up.

Conclusions—Immunologic failure criteria performed poorly in our setting and would have resulted in a substantial proportion of participants with suppressed HIV-1 VL being switched unnecessarily. These criteria also lacked sensitivity to identify participants failing virologically. Periodic viral load measurements may be a better marker for treatment failure in our setting.

Keywords

HIV/AIDS; antiretroviral therapy; immunologic monitoring

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Conflict of Interest:
The authors' declare none

Introduction

Guidelines for the use of antiretroviral therapy (ART) in resource-limited settings (RLS) state that immunologic monitoring of patients to determine response to treatment and the need to switch to a second line regimen may be used in settings where viral load testing is not available. [1] Specifically, the World Health Organization (WHO) guidelines for a public health approach to antiretroviral therapy suggest that a change in therapy be considered if: 1) the CD4 cell count falls below baseline in the absence of other concurrent infections, 2) the CD4 cell count falls to less than 50% of peak levels without coexistent infections, or 3) the CD4 cell count is consistently below 100 cells/mm^3. For either of the first two criteria, in an asymptomatic patient if the CD4 count remains above 200 cells/mm^3 switching therapy is not recommended. Viral load (VL) monitoring is not routinely available in most RLS due to the cost and technical requirements for the assay. However, access to VL measurement is likely to increase through the use of dried blood spots and simplified assays which overcome logistical barriers and may lower costs. [2]

Evaluation of the WHO immunologic criteria for response to antiretroviral therapy conducted in the British Columbia HIV/AIDS drug Treatment Program showed that immunologic monitoring poorly predicted virologic suppression. [3] Also, initial immunologic response to ART was shown to only modestly predict virologic response among ART recipients in Botswana.[4] However, little is known about the variability of CD4 cell counts in RLS where frequent co-infections may impact this already highly variable measure, and there have been no long term evaluations of the currently recommended immunologic failure criteria to examine their performance in African populations. Therefore, we evaluated the clinical utility of the current WHO immunologic criteria for treatment failure in terms of their ability to identify subjects who should be considered for switching to second line therapy on the basis of virologic failure criteria.

Methods

As of June, 2004, the Rakai Health Sciences Program began to offer free antiretroviral therapy (ART) to residents in rural Rakai District, southwestern Uganda, funded by the President's Emergency Plan for AIDS Relief (PEPFAR). The ART treatment program is provided using a mobile clinic service with biweekly visits to 16 regional health clinics. Eligibility for treatment is determined by CD4 cell count (<250 cells/mm^3) or WHO stage IV disease. Participants were seen weekly for the first month and then biweekly for 2 months and then monthly with adherence and HIV risk reduction behavior counseling provided before starting ART and at all follow-up visits. Immunologic monitoring was performed every 3 months for the first year on therapy and then every 6 months thereafter. Viral load testing became available at the Rakai Program laboratory in November, 2005 and was used for routine monitoring of all ART clients. Switching to second line treatment was considered if there was evidence of virologic failure after any adherence problems were addressed. The WHO recommended VL threshold for switch to second line therapy (VL>10 000 copies/ml) was used as a trigger and all potential clients failing first line therapy were discussed in a multi-disciplinary meeting attended by physicians, nurses and counselors.

As of March, 2008, 1133 participants who had initiated first line ART reached at least 6 months of follow-up. The initial regimen consisted of two NRTIs (zidovudine or stavudine plus lamivudine) and nevirapine or efavirenz. CD4 cell counts were measured initially by FACScount and later by FACSCaliber (Becton Dickenson, New Jersey, USA). HIV-1 viral load testing was performed using the Roche Amplicor 1.5 Monitor assay (Roche Diagnostics, Indiana, USA).

For the purposes of this analysis, immunologic failure was diagnosed if the participant met one of the following criteria: 1) persistent CD4 below 100 cells/mm^3, 2) a drop of CD4 cell count below baseline pre-treatment level, or 3) a drop of CD4 cell count of 50% from peak on treatment value all in the absence of an ongoing co-infection and after a minimum of 6 months of ART (chosen to ensure 2 follow-up CD4 tests and 1 VL measurement were performed). For criteria 2 and 3, the CD4 cell count must also fall below 200 cells/mm^3 to qualify as immunologic failure. Data were analyzed using three different virologic failure thresholds: 1) at least one RNA PCR result greater than 10,000 copies/ml during treatment follow up; 2) two or more RNA PCR results greater than 5,000 copies/ml; and 3) two or more results greater than 400 copies/ml. These thresholds were chosen for consistency with the WHO recommended switch threshold (VL 10 000 copies/ml), the South African National Department of Health treatment guidelines switch threshold (2 VL> 5000 copies/ml), and a more conservative threshold commonly applied in non RLS settings (2 VL>400 copies/ml). [5] We determined sensitivity and specificity, as well as positive and negative predictive value of the immunologic failure criteria to predict various definitions of virologic failure mentioned above. The effect of requiring a second, confirmatory CD4 measurement for all clients with evidence of immunologic failure was also assessed.

Results

In this analysis, we include the 1133 patients who received ART through the Rakai program and were followed for at least 6 months; the median follow up period was 20.2 months (IQR 12.4–29.5 months). Ten participants (0.9%) were lost to follow-up after completing at least 6 months of monitoring, six (0.5%) transferred to another program, 11 (1.0%) stopped ART due to side effects and 20 (1.8%) died. The median baseline CD4 was 153 cells/mm^3 (IQR: 69–214). Other baseline characteristics are listed in table 1. An initial immune response (rise in CD4 cell count by 6 months) occurred in 1012 (89.3%) participants. Virologic failure, according to the three study definitions (thresholds of 10 000 copies/ml at one time point, 5000 copies/ml or 400 copies/ml at two time points), occurred in 80 (7.1%), 36 (3.2%), and 112 (9.9%), participants, respectively (table 2).

Over the entire study period, a total of 125 (11.0%) developed immunologic failure as defined above. Using the virologic failure criteria of >400 copies/ml on two measurements, only 26 participants (2.3%) developed both immunologic and virologic failure (not necessarily at the same visit). 99 (8.7%) participants developed immunologic failure in the absence of virologic failure and would have been switched to a second line regimen if only the immunologic monitoring criteria were applied. Conversely, the majority of virologic failures (86/112, 76.8%) did not develop immunologic failure. The sensitivity/specificity of immunologic monitoring for predicting virologic failure (2 VL>400 copies/ml) was 23% and 90% percent respectively with the positive and negative predictive value being 21% and 91% percent. Table 2 illustrates the performance characteristics of the immunologic failure criteria at various VL cut off levels. Confirmation of the immunologic failure criteria with a follow-up CD4 measurement within 12 months reduced the number of false positive results but also greatly reduced the sensitivity of the immunological definitions to identify individuals failing virologically (table 2).

Discussion

This is the first study with long term follow-up evaluating the performance of immunologic monitoring criteria to identify individuals requiring a treatment switch in Uganda. Although earlier studies have shown the initial immunologic responses to ART poorly predict virologic responses, ours addresses the important question of the performance of commonly used immunologic failure criteria to identify individuals experiencing virologic failure on their first-line ART regimen.[3,4,6] This analysis of immunologic and virologic responses to ART in

Uganda suggests that immunologic monitoring, using the current WHO criteria, may result in unnecessary switching of treatment regimens. We also show the poor sensitivity of immunologic criteria in identifying individuals who had virologic failure and should be considered candidates for second line ART. Applying a more stringent definition for immunologic failure (confirmation of any of the immunologic failure definitions with an additional CD4 measurement) reduced the number of unnecessary switches but also compromised the sensitivity to identify individuals with virologic failure. Our findings are consistent with those of studies in Thailand and South Africa which also reported low sensitivity of immunologic criteria for detection of virologic failure (20.0% and 21.2% respectively) during follow up.[7,8]

Previous reports from non-RLS settings have suggested that the current WHO immunologic failure criteria performed poorly in identifying individuals who failed to respond virologically to antiretroviral therapy resulting in significant misclassification of treatment responses. Our report incorporates longer follow-up time in the Ugandan setting to examine the performance of these criteria in a rural based ART delivery program which monitors individuals both virologically and immunologically. We are concerned that the low sensitivity of immunologic failure criteria to predict virologic failure could result in prolonged undetected virologic failure. Prolonged virologic failure in the presence of ongoing drug pressure could result in significant accumulation of resistance mutations which could ultimately limit second line treatment options. Recent data from Malawi has revealed high levels of resistance among patients who were monitored immunologically with 16% of patients exhibiting pan-NRTI resistance greatly limiting second line treatment options.[9] Our results also suggest that individuals found to have immunologic failure in the absence of any co-infection should be considered for VL testing to avoid unnecessary switching to second line regimens.

Ultimately, the best strategies for monitoring ART in RLS will be determined through careful analysis of ongoing treatment cohorts providing additional data on the performance of various monitoring strategies to identify individuals in need of second line treatment options. Cost remains an important factor in examining options for policy makers deciding on the best monitoring strategies for their settings. Early, unnecessary switching to second line treatments incurs additional expense from increased drug costs and also limits the treatment duration of critically important first line regimens. Viral load testing remains a challenge for many RLS due to technological and economic obstacles. Newer technologies incorporating lower cost, robust and simple viral load monitoring options are urgently needed to improve our ability to deliver quality care to individuals receiving ART globally.

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Table 1

Baseline Characteristics of 1133 ARV program clients

Characteristic	Number (%)
Gender	
Male	405 (36)
Female	728 (64)
WHO Staging	
WHO Stage I	305 (27)
WHO Stage II	421 (37)
WHO Stage III	279 (25)
WHO Stage IV	128 (11)
Initial ART Regimen	
AZT/3TC/EFV	332 (29)
AZT/3TC/NVP	368 (33)
D4T/3TC/EFV	129 (11)
D4T/3TC/NVP	303 (27)
TDF/3TC/NVP	1 (0)
Age	Median (IQR)
years	35 (30–41)
CD4+ cell count	
cells/mm^3	153 (69–214)

Table 2

Performance of Immunologic Failure Criteria* to Predict Various Definitions of Virologic Failure among Clients Receiving First-line ART

	Immunologic/Virologic failure status									
	Immunologic only	**Immunologic & Virologic**	**Virologic only**	**None**	**Sens**	**Spec**	**PPV**	**NPV**	**Accuracy+**	**VL Fail Rate**
Virologic failure criteria										
At least 1 VL > 10,000 copies/ml	107	18	62	946	0.23	0.90	0.14	0.94	0.85	0.07
(with F/U confirmatory CD4)#	53	11	69	1000	0.14	0.95	0.17	0.94	0.89	0.07
At least 2 VL > 5,000 copies/ml	115	10	26	982	0.28	0.90	0.08	0.97	0.88	0.03
(with F/U confirmatory CD4)#	58	6	30	1039	0.17	0.95	0.09	0.97	0.92	0.03
At least 2 VL > 400 copies/ml	99	26	86	922	0.23	0.90	0.21	0.91	0.84	0.10
(with F/U confirmatory CD4)#	54	10	102	967	0.09	0.95	0.16	0.90	0.86	0.10

*Includes: 1) persistent CD4 < 100cells/mm^3 (i.e. CD4 < 100 at consecutive measurements from M6, but not more than 12 months apart); 2) any drop below baseline CD4 count from M6; 3) any single drop > 50% CD4 max from M6. For criteria 2 and 3, CD4 must also be < 200.

+Accuracy = (true positive results + true negative results) / total subjects

#Immunologic failure is defined as any of the above criteria that have been confirmed at a consecutive measurement within 12 months.

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