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Regional differences in predictive accuracy of WHO immunologic failure criteria

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We compared the performance of the WHO immunologic criteria for treatment failure among Uganda and American patients. Antiretroviral treatment-naïve patients with a CD4 T-cell count less than 200 cells/μl or AIDS at enrollment on a nonnucleoside reverse transcriptase inhibitors-based regimen for more than 1 year were selected. For all criteria, the positive predictive value was significantly higher in the American compared with the Ugandan patients. Population-specific guidelines should be developed using large African cohorts to identify more specific and sensitive criteria.

In industrialized countries, antiretroviral treatment (ART) efficacy is monitored through routine measurement of CD4⁺ cell counts and plasma viral load. Guidelines from the WHO on ART for HIV infection in resource-limited settings recommend the use of immunologic monitoring when viral load testing is not available [1,2].

Previous studies from sub-Saharan Africa have shown that the proposed criteria are neither sensitive nor specific [3–7]. We suspected that one of the reasons for poor performance in African patients is the high incidence of opportunistic infections, which could consequently impair the immune reconstitution of patients on ART [8,9].

We sought to evaluate the performance of the WHO immunologic criteria for treatment failure in a Ugandan and an American cohort and to compare the predictive values of these criteria in identifying patients on first-line ART with viral failure. We also examined the relative contribution of opportunistic infections on the performance of the criteria among the Ugandan patients.

The Infectious Diseases Institute (IDI) Research Prospective Observational Cohort is a closed research cohort of 559 patients, enrolled at ART initiation between April 2004 and April 2005 in Uganda. Details of the cohort have been published elsewhere [10].

The Johns Hopkins HIV Clinical Cohort (JHHCC) is an open observational longitudinal cohort database of HIV-infected patients in the USA, established in 1989 with over 6000

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Conflicts of interest

There are no conflicts of interest.

patients enrolled, with majority initiated on ART between 1999 and 2003. Details of the cohort have been published elsewhere [11].

Patients selected from both cohorts were as follows: ART-naïve at cohort enrollment; initiated on zidovudine/stavudine with lamivudine and efavirenz/nevirapine; baseline CD4⁺ cell count less than 200 cells/μl or clinical criteria of AIDS; and on ART for at least 1 year.

We compared the characteristics of the patients at ART initiation in both cohorts. Categorical and continuous variables were compared using chi-square and Mann–Whitney tests, respectively. To compare the performance of the WHO criteria in both cohorts, we identified the proportion of patients fulfilling at least one of the three criteria: CD4⁺ cell count less than 100 cell/μl after 12 months; more than 50% drop from CD4⁺ cell count peak; and CD4⁺ cell count lower than baseline [1]. We then obtained the proportion of patients with confirmed viral failure at the time they met any of the criteria. We calculated the positive and negative predictive values (PPV and NPV). Finally, we did a sensitivity analysis excluding patients who had ever had an opportunistic infection in the first year of ART in the IDI cohort. Ethical approval was obtained from the local Institutional Review Board committees.

We included 442 patients from the IDI cohort and 153 patients from the JHHCC. At ART initiation, a lower proportion of patients from the JHHCC were female (28.8 versus 69%, $P < 0.0001$), had a slightly lower median age [35 years, interquartile range (IQR) 30–41 years versus 39 years, IQR 35–44 years, $P < 0.001$], higher median BMI (22 kg/m², IQR, 19–26 kg/m² versus 20 kg/m², IQR 17–22 kg/m², $P < 0.0001$), lower median CD4⁺ cell count per microliter (42 versus 102, $P = 0.064$) and a higher proportion initiated on zidovudine with lamivudine and efavirenz (39% versus 26%, $P = 0.012$). A larger proportion of the IDI cohort experienced an opportunistic infection in the first year of ART (28.7% versus 13.7%, $P = 0.0002$). Tuberculosis was the most common opportunistic infection, with (4.7%) in the IDI cohort compared with (0.6%) in the JHHCC ($P = 0.021$).

The proportion of patients who fulfilled each of the criteria and had confirmed virologic failure in the IDI cohort versus JHHCC were as follows: 1.1% versus 6.5% ($P = 0.0002$) for criterion 1, 2.9% versus 37.9% ($P < 0.0001$) for criterion 2 and 4.1% versus 5.9% ($P = 0.354$) for criterion 3.

As shown in Table 1, the PPV for virologic failure in the IDI cohort and the JHHCC, respectively, was 13.5% and 52.6%, for criterion 1; 26.0% and 84.1%, for criteria 2; and 20.4% and 78.9%, for criteria 3. The NPV for criteria 1, 2 and 3 in the IDI cohort and JHHCC, respectively, was 87.6% versus 85.5%, 93.6% versus 84.4% and 93.5% versus 71.8%.

In a sensitivity analysis including only IDI cohort patients (71.3%) who did not experience an opportunistic infection, there was no significant difference in the PPV of this subgroup compared with the entire cohort for criteria 1 and 2: criterion 1, 13.0% versus 13.5% ($P = 0.835$); criterion 2, 26.0% versus 20.4% ($P = 0.06$); but, a significant difference for criterion 3 (20.4% versus 10.2%, $P < 0.0001$).

The WHO immunologic criteria selected higher proportions of virologically failing patients in the American than in a Ugandan cohort and had higher PPVs. Our results suggest that this difference is not due to the high rate of diagnosed opportunistic infections in the African setting, even though severe bacterial diseases often seen could also affect immunological response. Other possibilities include undiagnosed and untreated opportunistic infections, poor nutrition and differences in HIV subtypes. Studies from the east African region suggest that subtype D is associated with a faster decline in CD4⁺ cell count and increased risk of

mortality compared with subtype A [12,13] due to increased CD4⁺ cells activation and subsequent apoptosis [14]. It is important to evaluate the impact of host characteristics of the infected population on ART efficacy and viral subtype [15].

Published data suggest that, with immunological monitoring only, patients with confirmed viral failure are identified after significant accumulation of drug resistance [16].

Recent studies have shown that a viral load will reduce an early and unnecessary switch to second-line therapy, reduce accumulation of resistance and prevent drug resistance viral transmission by patients who are failing [17–19].

Our study limitations included, first, the differences in the data used in both cohorts; however, patients were identified during the roll-out of ART in both countries. Second, the younger age of JHHCC patients compared with IDI cohort patients could have influenced the higher immune response in JHHCC, as has been shown previously [20,21].

In summary, our data highlight the need for viral load measurements when identifying treatment failure in HIV-positive individuals on ART. Further research into the risk factors for the limited performance of these WHO immunologic criteria in resource-limited settings is needed. Population-specific guidelines should be developed using large African cohorts to identify more specific and sensitive criteria.

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Proportion of patients fulfilling the immunological criteria for treatment failure and proportion of patients with confirmed virologic failure.

Table 1

CD4 ⁺ cell count criteria	Immunologic failure			Confirmed virologic failure		
	IDI, n (%)	JHHCC, n (%)	P	IDI, n (%)	JHHCC, n (%)	P
<100 cells/ μ l after 12 months	37/442 (8.1)	19/109 (17.4)	<0.0001	5/37 (13.5)	10/19 (52.6)	0.003
>50% drop from peak	50/442 (11.3)	63/153 (41.2)	<0.0001	13/50 (26.0)	53/63 (84.1)	<0.0001
Less than baseline	88/442 (19.9)	11/153 (7.2)	0.034	18/88 (20.4)	9/11 (81.8)	<0.0001

IDI, Infectious Diseases Institute; JHHCC, Johns Hopkins HIV Clinical Cohort.