# Predictors of Long-Term Viral Failure Among Ugandan Children and Adults Treated With Antiretroviral Therapy

*Moses R. Kamya, MBChB, MMed, MPH,*† Harriet Mayanja-Kizza, MBChB, MMed, MSc,*† Andrew Kambugu, MBChB, MMed,† Sabrina Bakeera-Kitaka, MBChB, MMed,‡ Fred Semitala, MBChB,* Patricia Mwebaze-Songa, MBChB,† Barbara Castelnuovo, MD,† Petra Schaefer, AMBI,† Lisa A. Spacek, MD, PhD,§ Anne F. Gasasira, MBChB, MPH,* Elly Katabira, MBChB, FRCP,*† Robert Colebunders, MD, PhD,†‖ Thomas C. Quinn, MD,†§ Allan Ronald, MD,† David L. Thomas, MD,†§ Adeodata Kekitiinwa, MBChB, MMed,‡ and the Academic Alliance for AIDS Care and Prevention in Africa*

**Background:** HIV RNA viral load testing is costly and is generally unavailable in resource-limited settings. We identified predictors of viral failure and documented genotypic mutations in a subset of patients with viral failure after 12 months on antiretroviral therapy (ART).

**Methods:** From April 2004 to June 2005, consecutive treatment-naive patients beginning ART at a university clinic in Uganda were enrolled. Clinical information, CD4 cell count, and HIV RNA level were collected at baseline and every 3 to 6 months. Independent predictors of viral failure were identified using multivariate logistic regression. Genotypic drug resistance for 8 patients with viral failure at 12 months was measured at baseline and at 6 and 12 months.

**Results:** Five hundred twenty-six adults and 250 children (0 to 18 years of age) were started on first-line ART regimens and followed for 12 months. Outcomes could not be assessed in 13% of patients (79 died and 21 were withdrawn). Children were almost twice as likely to have viral failure compared with adults (26% vs. 14%; $P = 0.0001$). In adults, the sole independent predictor of viral failure was treatment with stavudine (d4T)/lamivudine (3TC)/nevirapine (NVP) versus zidovudine (ZDV)/3TC/efavirenz (EFV) (odds ratio [OR] = 2.59, 95% confidence interval [CI]: 1.20 to 5.59). In children, independent predictors of viral failure included male gender (OR = 2.44, 95% CI: 1.20 to 4.93), baseline CD4% <5 (OR = 2.69, 95% CI: 1.28 to 5.63), and treatment with d4T/3TC/NVP versus ZDV/3TC/EFV (OR = 2.46, 95% CI: 1.23 to 4.90). All 8 patients with viral breakthrough and genotypic drug resistance results had nonnucleoside reverse transcriptase inhibitor (NNRTI)– and 3TC-associated mutations.

**Conclusions:** These data demonstrate the effectiveness of ART in a low-resource setting. Children and patients of all ages taking the d4T/3TC/NVP regimen were more likely to have viral failure. Our data suggest that viral failure occurring 6 months or more after the start of ART regimens commonly used in Uganda is likely to be associated with NNRTI- and 3TC-resistant virus.

**Key Words:** antiretroviral therapy, predictors, resource-limited settings, viral failure

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Over the past 3 years, the use of antiretroviral therapy (ART) has markedly expanded in resource-limited settings. For example, in Uganda, ART scale-up started in July 2004, and an estimated 30,000 persons were receiving ART by September 2004. By March 2006, that number had increased sharply to 75,000, or approximately 61% of the HIV-1–infected patients in urgent need of ART (Uganda Ministry of Health).

The potential effectiveness of ART has already been demonstrated in the West, where HIV-1–related mortality has dropped dramatically.[1] Likewise, clear guidelines have emerged for monitoring ART by following clinical, immunologic (CD4 lymphocyte count), and virologic (HIV-1 RNA) responses.[2]

In resource-limited settings, there are data indicating that ART therapy can be effective in adults and children.[3–5] Many challenges remain, however, including profound immunosuppression at ART initiation,[3] a high prevalence of concurrent infection like tuberculosis,[6–8] and treatment interruption attributable to cost or supply.[9–11] In addition, the optimal means of monitoring ART has not been demonstrated in resource-limited settings.[12]

The World Health Organization (WHO) recommends monitoring ART clinically, with symptom- and ART drug regimen–directed laboratory assessment as needed. Where feasible, the WHO recommends immunologic monitoring of treatment efficacy.[13] HIV RNA viral load testing is costly and is generally unavailable in resource-limited settings. Patients

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From the *Department of Medicine, Makerere University, Kampala, Uganda; †Infectious Diseases Institute/Academic Alliance for AIDS Care and Prevention, Kampala, Uganda; ‡Pediatric Infectious Diseases Clinic, Mulago Hospital, Kampala, Uganda; §Department of Medicine, Johns Hopkins Medical Institutions, Johns Hopkins University, Baltimore, MD; and the ‖Institute of Tropical Medicine and University of Antwerp, Antwerp, Belgium.
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Correspondence to: Moses R. Kamya, MBChB, MMed, MPH, Department of Medicine, Makerere University, PO Box 7072, Kampala, Uganda (e-mail: mkamya@infocom.co.ug).

with viral failure may progress to drug resistance despite clinical well-being and/or immunologic recovery. We identified predictors of viral failure because that is the primary endpoint used to guide ART decision making in the West and the best measure of the risk of viral resistance.[14] We also documented genotypic mutations in a subset of patients with viral failure after 12 months on ART.

## PATIENTS AND METHODS

### Study Site

The Makerere University Infectious Diseases Institute (IDI) began providing expanded HIV care, training, and research at Makerere University Medical School and Mulago Teaching Hospital in Kampala, Uganda in March 2002. HIV care for more than 8000 patients occurs in the adult Infectious Diseases Clinic (IDC), which is situated on the ground floor of the newly built institute. By March 2006, >4000 adults were receiving ART at the IDC. Care for more than 5000 children and adolescents (and ART for >1300) occurs at the nearby Pediatric Infectious Diseases Clinic. Since 2004, all care has been provided at no charge and includes HIV counseling, treatment of HIV-related complications, laboratory testing (confirmatory HIV-1 testing, complete blood cell count, and CD4 lymphocyte count), cotrimoxazole prophylaxis for all, and ART for those with a CD4 count <200 cells/mm$^3$ or WHO clinical stage IV disease.

ART is provided according to WHO and Uganda Ministry of Health guidelines. The first ART for adults and adolescents is provided by the Global Fund (a generic combined formulation of stavudine [d4T; weight-adjusted], lamivudine [3TC], and nevirapine [NVP]) or by the US President's Emergency Plan for AIDS Relief (a combined formulation of zidovudine [ZDV] and 3TC plus efavirenz [EFV] purchased from the manufacturer). First-line ART regimens for children were d4T or ZDV plus 3TC plus NVP or EFV. Single-drug substitutions are permitted according to WHO guidelines: for example, d4T could be substituted for ZDV, and NVP could be substituted for EFV. The first-line regimen for children younger than 3 years of age substituted NVP for EFV. Adherence to ART was encouraged by at least 3 individual and group counseling sessions. In addition, patients who qualified for ART were encouraged to designate a family member or friend as a treatment supporter to aid with ART medication adherence and toxicity recognition.

Standard medical care for persons on ART includes monthly visits for counseling and to pick up prescriptions, at least quarterly physician evaluations, and laboratory testing (complete blood cell count/CD4 lymphocyte count every 6 months). Because of limited ART choices, our clinic practice is to postpone regimen changes for clinical, immunologic, or viral failure (vs. toxicity) to 12 months after starting, although emphasizing adherence at antecedent visits.

### Study Subjects, Procedures, and Measurements

From April 2004 to June 2005, 776 consecutive patients about to start their first course of ART were enrolled into a prospective observational cohort. Patients of all ages (pediatric cohort from 0 to 18 years of age and adult cohort ≥19 years of age) were enrolled if they fulfilled all the following eligibility criteria: (1) confirmed HIV-1 infection, (2) regular attendance (having attended at least 2 clinic visits in the past 6 months), (3) stable residence within a 20-km radius of Kampala, (4) willingness to be followed and exclusively receive HIV-1 care at the IDI for at least 2 years, and (5) provision of written informed consent or assent by parent/guardian. The study was reviewed and approved by the Makerere University Faculty of Medicine Research and Ethics Committee and the Uganda National Council for Science and Technology.

A standardized data collection form was completed for each patient at baseline and every 3 months. Clinical data included remote and current experience with opportunistic infections and related conditions. At every visit, we measured body weight and estimated adherence using the visual analog scale. Information on loss to follow-up, transfer, and death was kept for all patients.

Laboratory measurements included complete blood cell count, CD4 lymphocyte count, and plasma HIV-1 RNA level (viral load) every 6 months. CD4 lymphocyte testing was measured by FACSCount (Becton Dickinson, San Jose, CA) and, more recently, by FACSCalibur (Becton Dickinson), whereas the level of HIV RNA in plasma was determined by the Amplicor HIV-1 Monitor PCR Test, version 1.5 (Roche Diagnostics, Indianapolis, IN), with a lower limit of detection of 400 copies/mL. Complete blood cell counts were done by Coulter (Beckman Coulter ACT diff 2, Miami, FL), including hemoglobin (Hb), white blood cell count (WBC), total lymphocyte count (TLC), and absolute neutrophil count. All laboratory testing was performed at the Makerere University–Johns Hopkins University Core Laboratory, which follows Good Laboratory Practice guidelines, participates in regular proficiency testing (eg, UK National External Quality Assurance Scheme [NEQAS]) and virology quality assurance (VQA), and is certified by the College of American Pathologists. Genotypic drug resistance testing was conducted on 8 (7%) samples of 116 with a viral load >400 copies/mL at 12 months. The 8 patients constituted a convenience sample of 19 patients who had detectable viral loads at 6 and 12 months despite CD4 cell count increases (discordant CD4 cell and virologic responses). Sequencing was performed by Davis Sequencing at the University of California at Davis sequencing facility (Davis, CA). The HIVdb Program Sequence Analysis tool from the Stanford University HIV Drug Resistance Databases (Stanford, CA) was used to analyze the sequences for resistance-conferring mutations.

### Statistical Analysis

The primary outcome for this analysis was virologic failure, which was defined as an RNA level ≥400 copies/mL 12 months after starting ART or a change to second-line ART after an RNA level ≥400 copies/mL before 12 months. HIV RNA levels available between 245 and 485 days after the start of ART were considered as "12-month" virologic measurements for classification of the primary outcome. Patients for whom an alternate first-line regimen was substituted because

of toxicity were still considered to be on a first-line regimen and were not included in the viral failure category.

Statistical inferences were made separately for children and adults. Means were compared by the Student *t* test, and medians were compared by the Wilcoxon rank sum test. Proportions were compared by the $\chi^2$ test with the Yates correction or by the Fisher exact test when the cell number was <5. To identify predictors of virologic failure at 12 months, univariate and multivariate analyses were performed using logistic regression. Potential predictors included demographic factors (eg, age, gender), baseline clinical measurements (eg, HIV stage, initial ART regimens), and laboratory measurements (eg, CD4 cell counts, HIV RNA levels, Hb, mean corpuscular volume [MCV]). Patients for whom no 12-month virologic outcome was recorded (those who died or were withdrawn before 12 months) and those for whom 12-month HIV RNA measurements were unavailable for other reasons were excluded from the primary analysis. As part of a sensitivity analysis, multivariate analyses were repeated with excluded patients, including deaths, missing virologic data, and withdrawn patients, being classified as failures in an intention-to-treat analysis. Analysis was performed using SAS (SAS Institute, Cary, NC) and STATA, version 8.0 (Stata Corporation, College Station, TX) software.

## RESULTS

### Patients and Baseline Characteristics

Baseline characteristics of the 776 enrolled HIV-1–infected patients are described in Table 1. Of these, 526 were adults ≥19 years of age and 250 were children and adolescents aged 0 to 18 years. At baseline, most patients had advanced HIV disease (median CD4 count of 99 cells/mm$^3$ for adults and CD4% of 8.6 for children). The mean body weight was 55 (±10.5) kg for adults and 20 (±9.6) kg for children. The 776 patients were followed for up to 12 months: outcomes are summarized in Figure 1. Of the 776 patients, 79 (10%) died, 50 (63%) within 3 months after the initiation of ART. An additional 3 (0.4%) patients were lost to follow-up, 6 (0.8%) withdrew consent, or were excluded for other reasons, and 12 (1.5%) had missing virologic data, leaving 676 (454 adults and 222 children) for further analysis of ART response after 12 months.

**TABLE 1.** Baseline Characteristics of Study Participants Stratified by Age Group

| Characteristic | Age Group: Adults (n = 526) | Age Group: Children and Adolescents (n = 250) |
|---|---|---|
| Female gender (%) | 363 (69%) | 120 (48%) |
| Age in years, mean (SD) | 37 (8.4) | 9.2 (4.5) |
| WHO stage, no. (%) | | |
| Stage I | 2 (0.4%) | 0 (0%) |
| Stage II | 60 (11%) | 28 (11%) |
| Stage III | 283 (54%) | 187 (75%) |
| Stage IV | 181 (34%) | 35 (14%) |
| Initial ART regimen (%) | | |
| d4T-3TC-NVP | 386 (73%) | 66 (26%) |
| ZDV-3TC-EFV | 137 (26%) | 137 (55%) |
| ZDV-3TC-NVP | 1 (0.2%) | 33 (13%) |
| d4T-3TC-EFV | 2 (0.4%) | 14 (5.6%) |
| Karnofsky score, mean (SD) | 79 (11) | Not available |
| MCV (fL), mean (SD) | 85 (7.3) | 78 (8.2) |
| Hg (g/dL), mean (SD) | 11.6 (2.0) | 10.9 (1.8) |
| CD4 T cells | | |
| Median cells/mm$^3$ (IQR) | 99 (24 to 165) | 272 (8 to 516) |
| Median CD4% (IQR) | 5.4% (1.8% to 9.0%) | 8.6% (3.5% to 12.7%) |
| HIV-1 viral load ($\log_{10}$ copies/mL), mean (SD) | 5.3 (0.6) | 5.3 (0.8) |
| NVP or ZDV PMTCT history (%) | 21 (4.0%) | 9 (3.6%) |

PMTCT indicates prevention of mother-to-child transmission.

### Predictors of Viral Response

Viral suppression was noted in a greater proportion of adult patients (392 [86%] of 454) compared with children (164 [74%] of 222; $P < 0.001$). When patients who died or were lost to follow-up were also classified as ART "failures," however, the difference between adults (75%) and children (69%) was diminished ($P = 0.11$), chiefly because of a greater number of deaths in the adult patients. Overall, 74 (62%) of 120 patients with viral failure had viral loads of >10,000 copies/mL.

Compared with adults with viral suppression, a greater proportion of those with viral failure at 12 months were taking the d4T/3TC/NVP regimen (Table 2). Compared with children with viral suppression, a greater number of children with viral failure were male, had lower baseline CD4 lymphocyte (%) counts, and were taking the d4T/3TC/NVP regimen (Table 3).

In adults, the sole independent baseline predictor of viral failure was treatment with d4T/3TC/NVP versus ZDV/3TC/EFV (odds ratio [OR] = 2.59, 95% confidence interval [CI]: 1.20 to 5.59; $P = 0.02$). In children, independent predictors of viral failure included male gender (OR = 2.44, 95% CI: 1.20 to 4.93; $P = 0.01$), having a baseline CD4% <5 (OR = 2.69, 95% CI: 1.28 to 5.63; $P = 0.009$), and treatment with d4T/3TC/NVP versus ZDV/3TC/EFV (OR = 2.46, 95% CI: 1.23 to 4.90; $P = 0.01$) (see Tables 2, 3). The primary findings were similar when the multivariate analyses were repeated with the excluded patients (deaths plus missing virologic data plus withdrawn) classified as viral failures.

### CD4 T-Cell Responses

In adults, the CD4 lymphocyte count at 12 months was greater than the baseline value in 408 (90%) of 454 adult patients and remained the same or decreased from baseline in 46 (10%). The mean increase in the CD4 lymphocyte count at 12 months among patients with viral suppression (131.4 cells/mm$^3$) was not significantly different from that in patients with viral failure (123 cells/mm$^3$). In children, the CD4 lymphocyte count at 12 months was greater than the baseline value in 173 (98%) of 177 pediatric patients with available CD4 cell count data at baseline and 12 months and remained

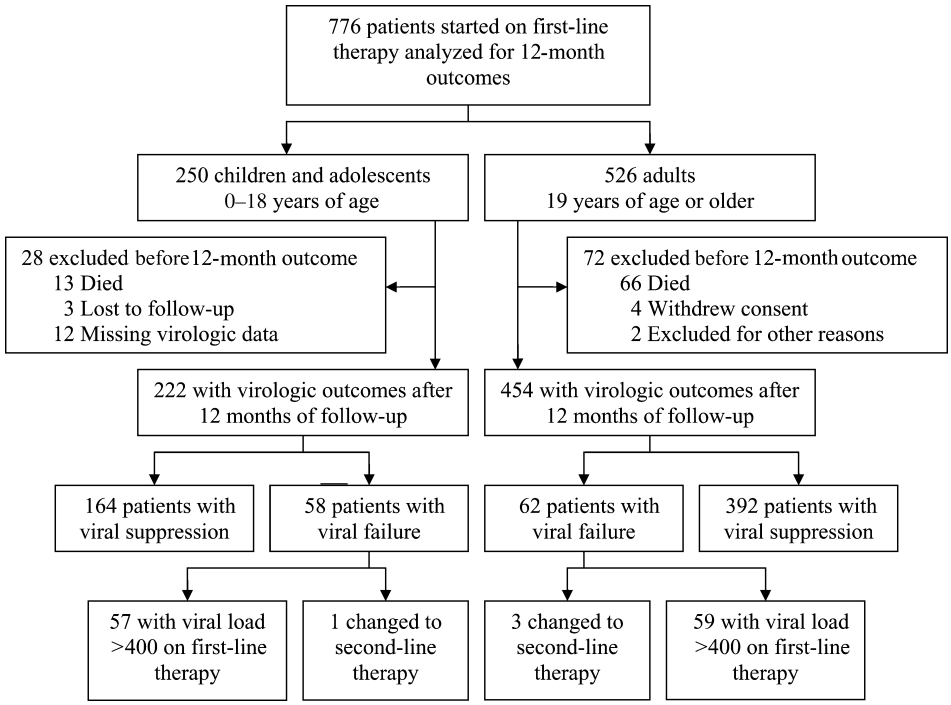


**FIGURE 1.** Profile of the study cohort at the Makerere University IDI, Kampala, Uganda.

the same or decreased from baseline in 4 (2%). The mean increase in CD4% at 12 months among pediatric patients with viral suppression (14.7%) was significantly greater compared with that in those with viral failure (11.3%; $P = 0.010$). CD4 lymphocyte responses were greater in children (0 to 18 years of age), including the subgroup with viral suppression.

## Weight Gain

At 12 months, a median body weight increase of 5.0 kg (interquartile range: 1.0 to 9.0) was observed among adult patients and a median weight increase of 3.5 kg (interquartile range: 2.1 to 5.1) was observed among children. In children and adults, using various weight gain cutoffs between baseline and 12 months, we found no significant differences between suppressed and unsuppressed patients.

## Adherence

Using the visual analog scale, more than 98% of our study participants reported 100% adherence at 6 months. In adults and children, there were no significant differences in reported levels of adherence at 6 months between those who had viral suppression compared with those with viral failure at 12 months.

**TABLE 2.** Predictors of Virologic Failure at 12 Months for 454 Adults Started on First-Line Therapy

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| **Baseline Predictor Variables** | **OR (95% CI)** | ***P*** | **OR (95% CI)** | ***P*** |
| Male gender | 1.19 (0.67 to 2.10) | 0.55 | 1.48 (0.77 to 2.83) | 0.24 |
| Age (per 5-year increase) | 0.86 (0.73 to 1.02) | 0.09 | 0.83 (0.69 to 1.02) | 0.08 |
| WHO stage | | | | |
| Stage III vs. stage I–II | 1.21 (0.48 to 3.05) | 0.68 | 0.93 (0.35 to 2.45) | 0.88 |
| Stage IV vs. stage I–II | 1.67 (0.64 to 4.34) | 0.30 | 1.19 (0.041 to 3.43) | 0.75 |
| Initial ART regimen | | | | |
| d4T-3TC-NVP vs. ZDV-3TC-EFV | 2.36 (1.12 to 4.94) | 0.02 | 2.59 (1.20 to 5.59) | 0.02 |
| Karnofsky score (per 10-point increase) | 0.90 (0.70 to 1.17) | 0.45 | 1.05 (0.78 to 1.41) | 0.77 |
| MCV (per 10-point increase) | 0.74 (0.50 to 1.11) | 0.15 | 0.78 (0.49 to 1.18) | 0.22 |
| Hb (per 1-g/dL increase) | 0.95 (0.84 to 1.10) | 0.55 | 0.99 (0.84 to 1.17) | 0.94 |
| CD4 count less than 100 cells/mm$^3$ | 1.60 (0.93 to 2.75) | 0.09 | 1.34 (0.74 to 2.40) | 0.33 |
| HIV-1 viral load (per $\log_{10}$ increase) | 1.63 (0.91 to 2.93) | 0.10 | 1.66 (0.89 to 3.11) | 0.11 |
| History of PMTCT use | 1.62 (0.52 to 5.02) | 0.40 | 1.43 (0.43 to 4.71) | 0.56 |

PMTCT indicates prevention of mother-to-child transmission.

**TABLE 3.** Predictors of Virologic Failure at 12 Months for 222 Children and Adolescents Started on First-Line Therapy

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| **Baseline Predictor Variables** | **OR (95% CI)** | ***P*** | **OR (95% CI)** | ***P*** |
| Male gender | 2.16 (1.15 to 4.04) | 0.02 | 2.44 (1.20 to 4.93) | 0.01 |
| Age (per 5-year increase) | 0.88 (0.62 to 1.24) | 0.46 | 0.91 (0.59 to 1.42) | 0.69 |
| WHO stage | | | | |
| Stage III vs. stage I–II | 2.19 (0.72 to 6.71) | 0.17 | 2.68 (0.71 to 10.2) | 0.15 |
| Stage IV vs. stage I–II | 0.75 (0.15 to 3.77) | 0.73 | 1.04 (0.16 to 6.72) | 0.96 |
| Initial ART regimen | | | | |
| d4T-3TC-NVP vs. ZDV-3TC-EFV | 2.62 (1.41 to 4.89) | 0.002 | 2.46 (1.23 to 4.90) | 0.01 |
| MCV (per 10-point increase) | 0.87 (0.61 to 1.25) | 0.46 | 0.98 (0.62 to 1.56) | 0.93 |
| Hb (per 1-g/dL increase) | 0.93 (0.79 to 1.10) | 0.40 | 0.96 (0.78 to 1.18) | 0.72 |
| CD4% <5% | 2.52 (1.32 to 4.81) | 0.005 | 2.69 (1.28 to 5.63) | 0.009 |
| HIV-1 viral load (per $\log_{10}$ increase) | 1.40 (0.88 to 2.22) | 0.16 | 1.25 (0.77 to 2.05) | 0.37 |
| History of PMTCT use | 1.14 (0.21 to 6.02) | 0.88 | 1.03 (0.14 to 7.37) | 0.97 |

PMTCT indicates prevention of mother-to-child transmission.

## Mean Corpuscular Volume Changes

Adults with viral failure had a significantly smaller mean increase in MCV of red blood cells (5.6 ± 2.4 fL) compared with those with viral suppression (14.5 ± 0.4 fL; $P < 0.001$). Similarly, children with viral failure had a significantly smaller mean increase in MCV (8.0 ± 1.2 fL) compared with those with viral suppression (12.0 ± 0.7 fL, $P = 0.0012$).

## Drug Resistance Data

Of the 116 participants (57 children and 59 adults) with detectable viral loads 12 months after ART, 8 genotypic drug resistance results were completed (Table 4). None of 4 patients with available genotypic testing at baseline had detectable antecedent resistant mutations. All 8 12-month specimens that were genotyped had nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations, with the most common being K103N (n = 5). All also had the 3TC-associated mutation M184V (n = 8). Two (25%) of the 8 patients had the thymidine analog mutation (TAM) T215Y.

# DISCUSSION

The results of this study underscore 2 important features of the sub-Saharan Africa ART roll-out: high early mortality and high early viral suppression.

**TABLE 4.** Drug Resistance Genotype Mutations and Predicted Phenotype Results for NRTI and NNRTI Resistance in 8 Treatment-Naive Participants at the IDI in Kampala, Uganda

| Patient No. (Age in Years) | Regimen | Genotype Mutations CD4 Count (Cells/μL); [Viral Load (Copies/mL)] | | | Predicted Phenotype Resistance (6 and/or 12 Months) |
|---|---|---|---|---|---|
| | | **Baseline** | **6 Months** | **12 Months** | |
| 1 (27) | NVP, 3TC, d4T | No mutations<br>116; [109,981] | NA<br>212; [10,796] | M184V, K103N<br>207; [4524] | 3TC, FTC, NNRTI |
| 2 (31) | NVP, 3TC, d4T | No mutations<br>54; [108,453] | M184V, K103N<br>140; [6132] | M184V, T215Y, K103N<br>114; [12,289] | 3TC, FTC, ABC, NNRTI |
| 3 (26) | NVP, 3TC, d4T | No mutations<br>30; [239,079] | M184V, K103N<br>135; [10,797] | M184V, G190A<br>156; [17,389] | 3TC, FTC, NNRTI |
| 4 (32) | NVP, 3TC, d4T | No mutations<br>6; [170,772] | V75I, M184V, Y181C<br>92; [69,091] | T69N, V75I, M184V, T215Y, Y181C<br>170; [234,077] | 3TC, FTC, ddI, d4T, TDF, ZDV, ABC, NNRTI |
| 5 (41) | NVP, 3TC, d4T | NA<br>105; [300,486] | M184V, K103N<br>102; [1038] | M184V, K103N,<br>282; [12,324] | 3TC, FTC, NNRTI |
| 6 (13) | NVP, 3TC, d4T | NA<br>279; [142,105] | M184V, L210D, G190A<br>324; [5699] | NA<br>351; [7009] | 3TC, FTC, NNRTI |
| 7 (16) | NVP, 3TC, d4T | NA<br>20; [122,143] | NA<br>226; [12,997] | M184V, K103N<br>194; [99,795] | 3TC, FTC, NNRTI |
| 8 (10) | EFV, 3TC, d4T | NA<br>12; [750,000] | NA<br>188; [NA] | T69S, M184V, Y188L<br>546; [84,491] | 3TC, FTC, NNRTI |

ABC indicates abacavir; DLV, delavirdine; NA, not available; NRTI, nucleoside reverse transcriptase inhibitor.

High early mortality reflects the advanced stage of HIV-1 infection at commencement of ART and the high prevalence of concurrent life-threatening infections such as tuberculosis[15–17] and *Cryptococcus neoformans*.[18] Paradoxically, immune reconstitution inflammatory syndrome (IRIS) may also contribute to high early post-ART mortality. In our study, 61% of the deaths occurred in the first 3 months, and those who died had lower baseline CD4 lymphocyte counts, Karnofsky scores, and blood Hb levels, reflecting the advanced stage of disease (data not shown). Similar findings have been reported by others;[17,19] collectively, these data highlight the need to begin ART before medical complications occur.

High early mortality notwithstanding, these data also demonstrate conclusively that ART can be effectively provided to adults and children in resource-limited settings. Among adults who survived to be evaluated 12 months after starting ART, high (86%) viral suppression was achieved, which exceeds real-world experiences in some resource-rich clinics and is consistent with other experiences in resource-limited settings.[20–24] If all those who were not followed or died ended up with viral failure, the overall effectiveness among adults (75%) and children (69%) was still consistent with results from other parts of the world.[25] A review of multiple African studies by Akileswaran et al[3] reported that an average of 73% of patients have an undetectable viral load by a median follow-up of 6 months. We cannot ascertain whether the proportion of viral suppression in our cohort would have been different if persons who died or were lost to follow-up had survived to have testing at 12 months.

Our data do not explain the full basis for high viral suppression. The strong emphasis that our clinic staff places on pretreatment counseling and the high self-reported adherence scores may contribute to achievement of viral suppression. Because unplanned interruptions of ART have been associated with viral failure, it is also possible that the constant provision of free ART contributed.[9,10] Our findings may be biased, because participants in our cohort received close medical attention. A recent cross-sectional study of 240 IDI adult patients not enrolled in the cohort showed a similar viral suppression rate (86%) 9 to 12 months after starting ART, however.

We detected differences in viral and CD4 lymphocyte responses between children and adults. Others have also reported that CD4 lymphocyte responses were more robust in younger adults.[26] Our study was not designed to explain the basis for these differences. Greater frequency of viral suppression seen in adults may reflect higher adherence or lower baseline viral loads compared with children.

In children and adults, we found that patients taking generic d4T/3TC/NVP were 2.5 times more likely to have viral failure compared with those taking branded ZDV/3TC/EFV. Our study was not randomized, and these results should be interpreted with caution. It is possible that the greater tolerability of ZDV/3TC/EFV compared with d4T/3TC/NVP might result in greater efficacy of this combination. Alternatively, generic formulations might have inferior quality compared with branded drugs. Pharmacokinetic studies are needed to confirm whether generic combinations provide the same bioavailability as branded drugs. Alternatively, our results may reflect unmeasured bias; in that case, a randomized, double-blind, controlled trial would be needed to answer the question. Compared with more immune-competent children, those who started ART with a CD4% <5 were more likely to fail therapy. A low CD4 cell count at the initiation of ART has been associated with a relatively poor probability of a good virologic response,[27] highlighting the need to start ART before children are severely immune suppressed. Our finding of greater viral failure among male compared with female children is unclear.

Genotypic drug resistance testing was performed on 8 samples (42%) from 19 patients who had CD4 cell increases and detectable viral loads at 6 and 12 months, and all 8 showed NNRTI and 3TC resistance. HIV-1 resistance occurs when ART is continued without viral suppression. This is notable because NNRTIs and 3TC have low genetic barriers to resistance. Our data suggest that viral failure occurring 6 months or more after the start of ART regimens commonly used in Uganda is likely to be associated with NNRTI- and 3TC-resistant virus. Our study, in line with larger studies, suggests that patients failing first-line ART require much more expensive and less easily accessible second-line drugs.

Given limited options for second-line ART, even more problematic in the long term could be the accumulation of TAMs in persons with viral failure and continued exposure to d4T or ZDV.[28] Thus, although immunologic responses provide important information regarding near-term risk of opportunistic infection and death, our data suggest that some adult patients, and possibly some pediatric patients, with virologic failure are initially missed by immunologic monitoring, supporting continued viral replication in the presence of drug pressure and development of additional resistance mutations. Further research is needed to assess if the clinical benefit of continued ART treatment outweighs the additional risk of TAMs. Future efforts should be focused on developing affordable methods for early detection of viral failure and consideration of less expensive drug resistance testing targeted at K103N and M184V mutations.

In this investigation, only single viral load and CD4 lymphocyte measurements were analyzed. Although this could lead to misclassification if results were altered by concurrent infection or measurement error, we found strong concordance between 6- and 12-month results for both tests. Moreover, results of analyses focused on 6-month outcomes generated essentially the same results (data not shown). It is also possible that these data are not generalizable to other settings. More than 90% of ART in sub-Saharan Africa was initiated within 2 years of our cohort, however, and includes the same compounds and patients with similar viral clades. For these reasons, and because of data already published, we believe that our cardinal findings may be valid throughout Africa. In particular, our data indicate that ART can be effectively given in sub-Saharan Africa and that future efforts should be focused on reducing early post-ART mortality (eg, by starting earlier and/or by preventing tuberculosis) and on developing affordable methods for early detection of viral failure and drug resistance.

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*All authors contributed to the design of the study and assisted with interpretation of the data and preparation of the manuscript. A. Gasasira assisted with verification and analyzing the data. M. R. Kamya led the manuscript preparation, with primary assistance from D. Thomas, R. Colebunders, T. Quinn, and L. Spacek.*

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