Evaluation of a Systematic Substitution of Zidovudine for Stavudine-Based HAART in a Program Setting in Rural Cambodia

Petros Isaakidis, MD, PhD, Marie-Eve Raguenaud, MD, MSc,* Thong Phe, MD, MSc,* Sam A. Khim, MD,* Sokhan Kuoch, MD,† Sopheap Khem,* Tony Reid, MD,‡ and Line Arnould, MD‡*

Objective: To evaluate a treatment strategy of substituting zidovudine (ZDV) for stavudine (d4T)-based highly active antiretroviral therapy (HAART), aimed at preventing d4T-associated toxicity, in a programmatic setting in rural Cambodia.

Methods: Survival probability, CD4 gain, anemia incidence, and factors associated with severe anemia were analyzed in a cohort of adult patients switched from d4T- to ZDV-containing regimens from March 2006 to March 2007.

Results: Among 527 patients systematically switched to ZDV after d4T-based HAART for a median of 18 months, 4 (0.8%) patients died, 2 (0.4%) were lost to follow-up, 18 (3.4%) were transferred out, and 503 (95.4%) remained on HAART. Median CD4 gain was +263.5 cells/μL (interquartile range: 89.25–369.5) at 24 months. Within 1 year after the switch, 21.9% and 7.1% of patients developed anemia (grades 1–4) and severe anemia (grades 3–4), respectively. Low body mass index (≤18) and low CD4 count (<200 cells/μL) at the time of switch were factors associated with severe anemia. Additional follow-up visits for laboratory monitoring and adherence counseling, increased absenteeism from work, and transportation costs for the patients were noted.

Conclusions: The switch strategy of substituting ZDV for d4T-based HAART led to satisfactory overall clinical outcomes. However, it resulted in a relatively high incidence of mild to severe anemia and increased burden for the program and the patients.

Key Words: zidovudine, stavudine, substitution, highly active antiretroviral treatment (HAART), resource-limited settings

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INTRODUCTION

The feasibility and efficacy of standardized highly active antiretroviral therapy (HAART) in resource-limited settings are increasingly being documented.[1–7] However, the limited number of available and affordable antiretroviral drugs in these settings is hampering the necessary treatment changes required in cases of toxicity, contraindications, or treatment failure. Stavudine (d4T) has been one of the most frequently prescribed nucleoside reverse transcriptase inhibitors (NRTIs) in initial first-line regimens in Cambodia, as in most resource-poor settings. Its availability at low-cost, fixed-dose combinations, its efficacy, and relatively low short-term toxicity that enhances patient adherence and limits the need for laboratory monitoring made it an attractive drug for standardized regimens.[8] However, there is increasing evidence that d4T is one of the NRTIs most associated with long-term mitochondrial toxicity, and it is therefore no longer recommended by World Health Organization (WHO) as the preferred NRTI.[9–11]

Very limited evidence regarding treatment strategies to prevent the d4T-associated toxicity in resource-restricted settings is available.[12,13] Meanwhile, zidovudine (ZDV) is becoming increasingly affordable and available despite concerns about its short-term tolerability, especially the risk of anemia among patients with advanced disease, women, and individuals with low body mass index (BMI).[14,15] A promising strategy to prevent d4T toxicity has been suggested based on experts' advice: a switch from d4T to ZDV after several months of HAART.[12,13] The rationale for this change is to prevent the long-term toxicities associated with d4T, although retaining its benefits in the short term, taking into account the potential risk of anemia of initial ZDV-based regimens. Evidence for this switch strategy is very limited, but one study, with a small cohort of patients and a switch after 6 months, found the incidence of anemia to be less than expected.[12] Our study had a larger cohort of patients and the switch occurred later so that it provides additional evidence regarding the advisability of the switch strategy.

Since March 2006, the treatment protocol for HIV/AIDS patients in Takeo Hospital, a referral hospital in rural Cambodia run by Ministry of Health and supported by Medecins Sans Frontières, implemented a systematic switch from a d4T- to a ZDV-based regimen, after at least 6 months of HAART. The purpose of this study is to describe the results of the switch strategy, including survival indicators, the incidence of side effects, notably anemia and its risk factors, and adherence and implications for clinical programing and for the patients.

METHODS

Study Design

This was a retrospective, observational study using data routinely collected at each consultation and entered prospectively

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From the *Médecins Sans Frontières OCB, Phnom Penh, Cambodia; †Chronic Diseases Clinic, Donkeo Provincial Referral Hospital, Ministry of Health, Takeo, Cambodia; and ‡Médecins Sans Frontières OCB, Brussels, Belgium.

Correspondence to: Dr. Petros Isaakidis, MD, PhD, Médecins Sans Frontières OCB, 72, Street 592, PO Box 840, Phnom Penh, Cambodia (e-mail: msfb-phnom-penh-med@brussels.msf.org).

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into FUCHIA monitoring software (Follow-Up and Care of HIV Infection and AIDS, Epicentre, Paris).

The study was approved by the Ethical Review Board of Médecins Sans Frontières on October 1, 2007 and by the National Ethics Committee for Health Research of Cambodia on October 8, 2007.

Setting

Médecins Sans Frontières, in collaboration with the National Center for HIV/AIDS, Dermatology, and STDs and the Ministry of Health, has been supporting the Chronic Disease Clinic of the Donkeo Referral Hospital in Takeo Province, South Cambodia, since 2003. An HAART was offered free of charge to patients either at WHO stages I, II, or III with CD4 count ≤200 cells/μL or at WHO stage IV (AIDS) irrespective of CD4 count as per WHO recommendations and the national HAART protocol. Most patients were initiated on a fixed-dose combination of stavudine–lamivudine–nevirapine whereas in case of contraindications or intolerance, alternative regimens were offered [including ZDV, tenofovir (TDF), efavirenz, and protease inhibitors]. ZDV- or TDF-based HAART regimens were not prescribed as initial regimens because of concerns about the tolerability of ZDV, especially the risk of anemia, and because of the limited availability of TDF in Cambodia.

Study Population

The study population included all adults, aged 15 years or more, who were systematically switched from d4T- to ZDV-based HAART after at least 6 months of treatment. Nonnaive patients, those with less than 3 months of follow-up after the switch and those with hemoglobin (Hb) less than 8.0 g/dL, and patients with blood test results not recorded in their medical files were excluded from the analysis.

Switch Strategy

From March 2006, all new patients initiated on d4T-based HAART were eligible for a systematic switch to ZDV after 6 months and all patients in the cohort already on a d4T-based HAART regimen for at least 6 months were switched to ZDV-based HAART. If in subsequent measurements Hb decreased by 30% from the previous level or from baseline or peak level, ZDV was ceased and a TDF-based regimen was offered. Patients with other side effects were also changed from ZDV. From the time of the drug switch, each patient was required to come on a biweekly basis during the first month, then on a monthly basis till 6 months, and then every 2–3 months thereafter for monitoring and drug education.

Outcome Measurements

Outcomes including death, loss to follow-up, and transfer out were recorded at the end of the observation period, June 30, 2007. CD4 counts were performed at baseline and every 6 months thereafter, using flow cytometry (Facscount; Beckton Dickinson, San Jose, CA) at the Donkeo Referral Hospital, in Takeo. Hb measurements were taken at the time of switch, at weeks 2, 4, 8, and 12, at month 6, and every 6 months thereafter. Anemia was graded according to the AIDS Clinical Trials Group criteria[16]; grade 1: Hb 8.0 to <9.5 g/dL, grade 2: 7.0 to <8.0 g/dL, grade 3: 6.5 to <7.0 g/dL, and grade 4: <6.5 g/dL. The incidence rate of anemia was defined as the number of patients with at least one follow-up Hb <9.5 g/dL (threshold for grade 1 anemia) per 100 person-years of at-risk follow-up. The follow-up period, during which the patient was considered at risk, started on the day of the treatment change (d4T to ZDV) and continued to the date of the last follow-up or date of death or loss to follow-up or the date of the first blood cell count showing a value below the corresponding threshold.

Statistical Analysis

Overall survival probability and anemia-free survival probability were estimated using the Kaplan–Meier method. Incidence rates of ZDV-associated hematological adverse events were recorded. Anemia greater than grade 2 (serum Hb value under 7.0 g/dL) within 12 months after ZDV initiation was designated as the dependent variable for identifying potential risk associations. The measures of risk were determined by crude odds ratios and adjusted odds ratios. Odds ratios were adjusted using multivariable logistic regression, and all related P values were based on the Walds test. The χ^2 test for linear trends was also used. The level of significance was set at $P = 0.05$ or less, and 95% confidence intervals (CIs) were used throughout. The analysis considered data until June 30, 2007. Analyses were performed using STATA 7.0 (STATA Corp, College Station, TX).

RESULTS

Patients and Follow-up

From August 2003 to March 2007, 1693 patients above 15 years of age had started HAART, 1638 of them on a d4T-based regimen. Nine hundred twenty patients had stopped d4T and were taking a ZDV-based regimen for any reason by June 2007. Of 689 patients, who were switched to ZDV systematically and not because of toxicity or other reasons, 527 were included in the analyses. Patients excluded from the analyses included 104 patients with less than 3-month follow-up after the treatment change, 45 patients with less than 2 Hb values after the treatment change, and 13 patients nonnaive for HAART (Fig. 1). The main baseline and follow-up characteristics of the remaining 527 patients are shown in Table 1. Seventeen patients (3.0%) had anemia at the time of switch, including 7 with greater than or equal to grade 2 anemia. The enrollment of these 7 patients represented a treatment protocol deviation, and they were excluded from the analysis of anemia over time. The median time on d4T before switching to ZDV was approximately 18 months. The median follow-up after ZDV initiation was approximately 10 months.

Clinical and Immunological Outcomes and Patient Survival

Among the 527 patients included in the analysis, 4 (0.8%) patients died, 2 (0.4%) were lost to follow-up, 18 (3.4%) were transferred to another health facility, and 503 (95.4%) remained on HAART at the end of the observation period (Table 1). Causes of death included severe anemia for 1 patient, severe opportunistic infection for 2 patients, and unknown for 1 patient.

Estimates of survival by the Kaplan–Meier method were 0.9981 at 12 months (95% CI 0.9865 to 0.9997) and 0.9937 at 24 months (95% CI 0.9807 to 0.9980) when death and loss

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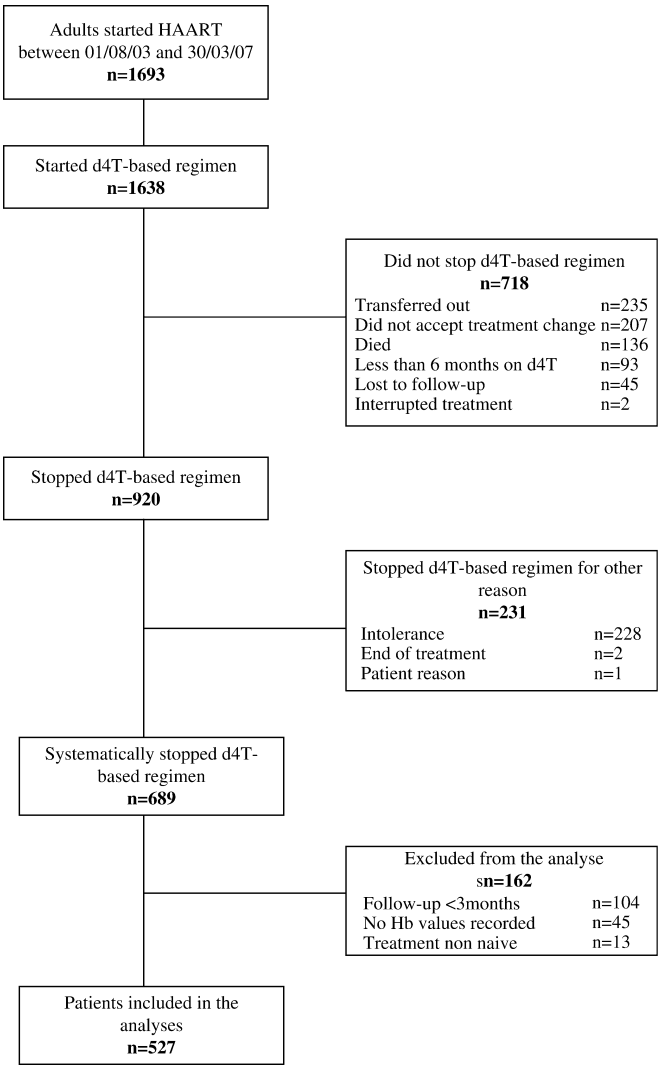

FIGURE 1. Patient flow chart.

to follow-up events were taken into account. The median CD4 at the time of HAART initiation was 61 cells/μL [interquartile range (IQR): 16–148.5]. Among patients with available CD4 count at the time of switch (n = 527), median CD4 gain was found to be +121.5 cells/μL (IQR: 81.25–177.75) at 6 months (n = 518), +180 (IQR: 124–249) at 12 months (n = 507), and +263.5 (IQR: 189.25–369.5) at 24 months (n = 386).

One hundred fifty-six (29.8%) patients experienced a drop in CD4 count between the time of switch and the end of the observation period. However, only 5 patients had a drop in CD4 that met WHO criteria for immunological failure.[9] Two patients had a detectable viral load (VL), 2 had an undetectable VL, and 1 was still on follow-up at the time of the analysis.

Incidence and Characteristics of Anemia Over Time

Overall, 114 (21.9%) patients developed an episode of anemia of greater than or equal to grade 1 within 1 year after starting ZDV (Table 2) whereas 7.1% of them developed severe anemia (grades 3–4). The overall incidence rate of grades 1–4 anemia was 31.83/100 person-years (95% CI 26.7 to 37.9), and the incidence rate of severe anemia was 10.0% (95% CI 7.3 to 13.7) (Table 3).

Figure 2 shows the Kaplan–Meier estimate of the probability of being anemia free at 1 year after starting the ZDV-based regimen to be about 0.75.

TABLE 1. Baseline and Follow-up Characteristics of HIV-Positive Patients Who Were Systematically Switched From D4T- to ZDV-Based Regimen (n = 527)

Male/female, n (%)	227/300 (43/57)
Age, yrs, median (IQR)	35 (30–40)
On CMX at time of switch, n (%)	172 (33)
WHO clinical stage at time of switch, n (%)	
I	7 (1)
II	50 (9)
III	150 (29)
IV	320 (61)
CD4 count, mm^3, at time of switch	
0–99	18 (3)
100–199	110 (21)
200–499	327 (62)
≥500	72 (14)
CD4 count, mm^3, at time of switch, median (IQR)	308 (202–419)
Body mass index, kg/m^2, n (%)	
<16.0 severe malnutrition	6 (1)
16.0–16.9 moderate malnutrition	6 (1)
17.0–18.0 mild malnutrition	86 (16)
>18.0 normal nutrition	429 (81)
HAART regimen, n (%)	
3TC + d4T + EFV	43 (8)
3TC + d4T + NVP	484 (92)
Hb level, g/L, median (IQR)	12.8 (11.6–14.0)
Anemia grade	
>9.5 (normal)	510 (97)
8.0 to <9.5 (grade 1)	10 (2)
7.0 to <8.0 (grade 2)	6 (1)*
6.5 to <7.0 (grade 3)	1 (0)*
<6.5 (grade 4)	0
No. days on d4T before ZDV switch, median (IQR) (range)	546 (428–725) (91–116)
No. days on ZDV before stopped, n = 54, median (IQR) (range)	109.5 (74.75–231.5) (6–1030)
Follow-up until ZDV stop or until last consultation or death	
Cumulative, person-days	168,604
Per patient, d, median (IQR) (range)	309 (187–428) (6–1087)
Outcomes at study termination, n (%)	
Dead	4 (0.8)
Alive	503 (95.4)
Lost to follow-up	2 (0.4)
Transferred out	18 (3.4)

CMX, co-trimoxazole; EFV, efavirenz; NVP, nevirapine; 3TC, lamivudine
*Protocol deviation: eligibility criteria included Hb 8.0 g/dL.

Factors Associated With Incident Anemia

In univariate analysis, age, sex, and duration on d4T-based regimen before switch were not associated with the risk

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TABLE 2. Incidence of Anemia Within 1 Year After Initiation of ZDV-Containing Regimen (n = 520)

Most Severe Episode	n (%)	Cumulative, n (%)
Grade 4 (<6.5 g/dL)	28 (5.4)	28 (5.4)
Grade 3 (6.5 to <7.0 g/dL)	9 (1.7)	37 (7.1)
Grade 2 (7.0 to <8.0 g/dL)	12 (2.3)	49 (9.4)
Grade 1 (8.0 to <9.5 g/dL)	65 (12.5)	114 (21.9)

Description of the most severe episode experienced by each patient based on all Hb measurements at scheduled and nonscheduled visits, excluding 7 patients with baseline Hb < 8.0 g/dL at the time ZDV was started.

of grades 3–4 anemia. The odds of developing severe anemia within 1 year after the switch were higher in patients with CD4 count less than 200/mm^3 at the time of ZDV initiation, in malnourished patients, and in patients on co-trimoxazole prophylaxis at the time of ZDV initiation (Table 4). There was a significant trend of the odds of anemia with decreasing BMI.

All variables used in the univariable analysis were included in a multiple regression model, except for co-trimoxazole prophylaxis. As the program protocol recommended the administration of co-trimoxazole prophylaxis based on CD4 count, we checked for multicollinearity between these 2 variables. The correlation coefficient between co-trimoxazole prophylaxis and CD4 category was found to be 0.75, and it was, therefore, removed from the analysis.

In the multivariable analysis, the odds of severe anemia for patients with less than 200 CD4 cells/mm^3 when starting ZDV-based regimen were 2.40 (95% CI 1.19 to 4.87) greater than for those with more than 200 CD4 cells/mm^3. Malnutrition, as defined by BMI less than or equal to 18.0 kg/m^2, was found to be significantly associated with occurrence of severe anemia (odds ratio = 2.72 CI 1.29 to 5.72) (Table 4).

In an attempt to distinguish anemia induced by ZDV from that related to concomitant diseases, we looked at the clinical events reported within 1 month of the lowest Hb level. Of the 40 patients with grades 3–4 anemia, 4 had an opportunistic infection: 3 pulmonary tuberculoses and 1 severe bacterial pneumonia.

ZDV Discontinuation and Mortality

Within 1 year after the switch, ZDV was stopped in 51 patients (9.8%) of the study population. The overall rate of ZDV discontinuation was 54/461.61 person-years or 11.70/100 person-years (95% CI 8.96 to 15.27). Forty-three patients discontinued ZDV because of intolerance: 38 cases of intolerance were due to anemia, 2 had lactic acidosis, 2 developed myopathy, and 1 developed neutropenia with anemia. Only mild and self-limited cases of gastrointestinal intolerance (nausea and vomiting) were observed. No cases of ZDV-associated gastrointestinal intolerance requiring treatment discontinuation were recorded in our program.

One patient with grade 3 anemia died 91 days after ZDV initiation and 33 days after developing anemia. Mortality rate was therefore 1/40 for patients who developed at least one episode of grade 3 or 4 anemia.

TABLE 3. Overall Rates of Incident Anemia After Initiation of ZDV-Containing Regimen (n = 520)

Anemia Grade	No. Patients	No. Person-Years	Rate Per 100 Person-Years (95% CI)
Grades 1, 2, 3, 4	127	398.95	31.83 (26.75 to 37.88)
Grades 2, 3, 4	56	398.95	14.04 (10.80 to 18.24)
Grades 3, 4	40	398.95	10.03 (7.35 to 13.67)

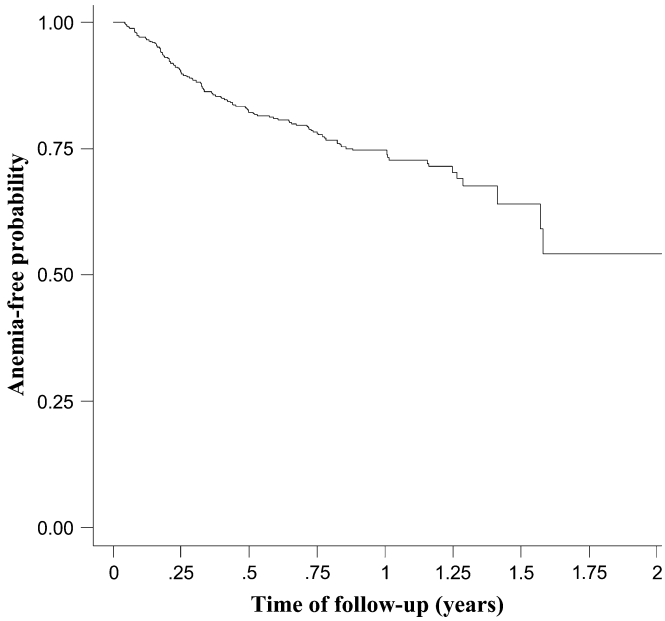

FIGURE 2. Kaplan–Meier curve showing the grades 1–4 anemia-free probability among the patients systematically switched to ZDV-based regimen.

Program Challenges

The introduction of the systematic switch resulted in a number of changes in the clinic including: (1) adjustments in drug forecasting and procurement to ensure constant supply of antiretrovirals and reagents for blood tests and blood for transfusions, (2) simplification and rationalization of the flow of patients to absorb the increased patient load coming for the extra consultations, (3) organization of additional, specific counseling sessions for patients undergoing the regimen change, (4) elaboration of patient health educational tools on the d4T- and ZDV-associated adverse events.

For patients previously on HAART for many months and followed up on a 3-monthly basis, the treatment switch represented an increase in scheduled appointments, which disturbed their daily routine. These extra appointments led to increased absenteeism from work and increased transportation costs although the latter costs were mostly covered by nongovernmental organizations. The majority of patients understood the rationale for the treatment change and agreed upon the additional follow-up visits for clinical and laboratory monitoring. However, 207 patients did not accept the switch mainly because of the problems associated with the additional follow-up

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TABLE 4. Factors Associated With Severe Anemia (grades 3, 4) Within 1 Year After Switching to ZDV-Containing Regimen, n = 520

Factors Present at Time of ZDV Switch	Grades 3 and 4 Anemia Cases/patients (%)	Univariable Model			Multivariable Model		
		OR	95% CI	*P*	OR	95% CI	*P*
Sex							
Male	18/224 (8.0)	1.0	—	—	1.0	—	—
Female	19/296 (6.4)	0.78	0.40 to 1.53	0.48	0.82	0.40 to 1.70	0.596
Age (yrs)							
<50	35/494 (7.1)	1.0	—	—	1.0	0.18 to 3.88	0.81
≥50	2/26 (7.7)	1.09	0.25 to 4.81	0.91	0.83	—	—
CD4 cells							
≥200/mm^3	21/393 (5.3)	1.0	—	—	1.0	—	—
<200/mm^3	16/127 (12.6)	2.55	1.29 to 5.06	**0.007**	2.54	1.21 to 5.34	**0.013**
BMI (kg/m^2)							
>18.0	24/424 (5.7)	1.0	—	—	1.0	—	—
≤18.0	13/96 (13.5)	2.61	1.28 to 5.34	**0.009**	2.84	1.33 to 6.07	**0.007**
Duration on d4T-based regimen							
>18 mos	19/283 (6.7)	1.0	—	—	1.0	—	—
12–18 mos	12/162 (7.4)	1.11	0.53 to 2.35	0.782	0.82	0.36 to 1.84	0.627
≤12 mos	6/75 (8.0)	1.21	0.46 to 3.14	0.698	0.79	0.28 to 2.21	0.660
Co-trimoxazole prophylaxis							
No	18/352 (5.1)	1.0	—	—	—	—	—
Yes	19/168 (11.3)	2.37	1.21 to 4.64	**0.012**	—	—	—

All variables were included in the multiple regression model except for co-trimoxazole prophylaxis. The *P* value for the likelihood ratio test for the model was 0.0352. All bold values indicate statistically significant factors.
OR, odds ratio.

visits or their physician/counselor concluded that they did not fully understand the rationale of this protocol change.

DISCUSSIONS

To our knowledge, this is the first study describing the results of a systematic switch from d4T to ZDV in a large cohort of patients after having received an initial HAART regimen containing d4T for a relatively long time (median time 18 months). The overall survival and the immunological response in this cohort of patients are comparable to other studies in resource-poor settings,[2–6] and severe side effects, besides anemia, were relatively uncommon. However, clinically significant anemia and severe anemia requiring a treatment change from ZDV occurred fairly frequently. Although patients generally understood the rationale for switching and agreed to the extra visits to monitor side effects, the perceived burden of extra visits and the consequent work absenteeism were not acceptable for many others.

Regarding anemia, the median time found for development of grades 3–4 anemia was similar to that reported in a comparable setting in Cambodia.[12] The low prevalence of diagnosed concomitant infections, at the time of the lowest Hb level, suggests that most cases of anemia detected were related to drug toxicity.

Risk factors for human immunodeficiency virus (HIV)–related anemia reported in the literature include advanced HIV disease, female sex, African origin, low BMI, and older age.[17–22] Despite the fact that our study population was relatively young (median age 35), with a median Hb at the time of the switch of 12.8 g/dL, 75% of them had CD4 counts above 200, 81% presented with normal BMI, and only one third of them were on co-trimoxazole prophylaxis at the time of the switch, still an important proportion of them developed anemia. In a prospective study in West Africa on a cohort of 498 HIV-infected patients, an incidence rate of 9.6/100 person-years grades 3–4 anemia was reported.[18] Despite the similar rate observed here, their study population was different with respect to co-trimoxazole intake[23] (80% had received at baseline versus 33% in our study population) and prior history of HAART treatment.

In our cohort, we observed that the risk of developing severe anemia was related to malnutrition as measured by BMI less than 18 kg/m^2 and low CD4 count less than 200/mm^3. Although the management of severe anemia requiring blood transfusion can be difficult in finding a blood donor, the mortality rate was very low in our program setting with 1 death.

Given increasing evidence of d4T-associated long-term toxicity, clinicians, program managers, and policy makers want to address this issue, and the switch strategy was developed as a possible solution. There are valid arguments for adopting it. Prescribing a generally well-tolerated d4T-based regimen for a few months before switching to ZDV allows for easier stabilization of the patients. This is particularly important in contexts where many patients have advanced HIV disease before starting HAART. These patients would be at higher risk of developing anemia, and it would be difficult for clinicians to differentiate symptoms of anemia due to ZDV toxicity from those due to HIV-related illnesses.

Although a recent publication suggested that prior HAART experience was protective for development of

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ZDV-induced anemia,[12] the incidence of anemia in our study was comparable to that occurring among populations who were initiated on ZDV,[24–26] and the duration on d4T-based regimen before switch was not associated with the occurrence of anemia.

There are several program management concerns regarding a switch strategy. Patient adherence could potentially be challenged. As a change in treatment regimen might result in confusion over pill intake, carefully planned counseling sessions are required and toxicities of drugs have to be discussed with the patient in detail. In addition, as most patients are on d4T-based regimens that called for 3-monthly visits, over many months or years, the intensified follow-up required for clinical and laboratory monitoring became a burden for them. In fact, 207 patients declined the switch, claiming that the foreseen increased absenteeism of work was challenging. Despite this, among patients who accepted the treatment change, we did not experience an increase in missed or delayed appointments. This was probably the result of the additional support given to these patients, including financial support for transportation. Both the additional counseling and increased laboratory monitoring required more clinic appointments, all adding significantly to the workload. This issue has to be considered as a cost of making the switch.

Huffam et al[12] showed a relatively high proportion (38%) of patients experiencing a drop in CD4 on at least one occasion after switching from d4T to ZDV, highlighting a possible negative impact from a change in HAART regimen. In our study, 156 (29.8%) patients experienced a drop in CD4 from the time of switch to the end of the observation period. Even though only few patients were diagnosed with virological failure, we cannot exclude that the ZDV switch might have led to a suboptimal CD4 increase and to treatment failures that we could not detect. The limited access to VL testing in our program setting did not allow for systematic VL measurement in patients switched to ZDV and thus did not allow for accurate evaluation of treatment effectiveness. It is one more example of the need for readily available, affordable VL technologies in resource-constrained settings.

Finally, of major concern is the fact that for patients who developed severe anemia and had to be switched to TDF after having received d4T and ZDV, the sequence of future HAART regimens in the event of treatment failure will be difficult.

On the other hand, TDF is a potent and safer alternative to both d4T- and ZDV-based standardized first-line regimens.[9] Its use as a core drug in first-line regimen could avoid the problems commonly encountered with other NRTIs. Although laboratory monitoring is required with TDF, associated toxicities are less frequent than those related to d4T and ZDV.[27,28] This points to the need to develop low-cost, fixed-dose combinations containing TDF for the future.

The timing of a switch is still in question. In the previous study, patients were switched at 6 months whereas our median switch timing was at 18 months.[12] Choosing the optimum timing requires balancing the d4T toxicity avoided by the switch against the increased rate of ZDV-induced anemia and the extra burdens for patients and the programs.

There are some limitations to the study including the fact that it was based on program data and did not allow for measurement of the benefits of avoiding d4T toxicity. Information on concomitant OIs could be incomplete, and a greater proportion of the anemia observed could then be attributed to opportunistic infections than ZDV toxicity. The relatively high number of patients who declined the switch might have influenced the results. We compared selected characteristics between this group and the study population, at different time points (6, 12, and 18 months after HAART initiation) (data not shown). Statistically significant differences found were as follows: a higher CD4 count at month 18, a higher proportion of women, and a lower proportion of patients on efavirenz-based regimen at 6 and 12 months, among patients who accepted the switch. It is likely that the difference in CD4 counts between these 2 groups had no clinical significance as it was observed at only one time point, and all CD4 count means were above 300 cells/μL. Efavirenz in our setting was mostly prescribed concomitantly with antituberculosis treatment. This suggests that there were more patients with tuberculosis in the group that declined the switch, which could have led to an underestimation of anemia in the study population, as tuberculosis is associated with a greater risk of anemia. On the other hand, the higher proportion of women in our study population may have led to an overestimation of anemia, as female sex is a known factor for anemia. However, in the univariable and multivariable analyses, female sex was not found to be associated with severe anemia in our setting.

The study design did not allow to assess the best time of switch, and we had to rely upon expert advice. Although program implications for patient follow-up were reported, patient satisfaction was not assessed. Randomized controlled trials could produce stronger evidence on the best switch strategy in terms of safety and efficacy, especially regarding long-term treatment success.

Our study showed that after 18 months of d4T-based HAART, a systematic switch to ZDV in a large cohort of patients resulted in a relatively high incidence of anemia and an unexplained drop in CD4 counts in a significant number of patients. Programmatic challenges observed included an increased laboratory monitoring and adherence counseling, a heavier workload for staff, and a burden for patients. Nevertheless, satisfactory overall clinical and immunological outcomes were recorded in this cohort of patients. Programs in rural areas in resource-limited settings may neither have the laboratory capacity for frequent Hb and VL measurements nor the organizational capacity for an effective implementation of the switch. If a strategy for substituting ZDV for d4T-based HAART is to be applied in resource-limited settings, then ZDV-associated adverse events and context-specific programmatic challenges need to be weighed against the expected benefit of decreased long-term d4T toxicity.

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