Evidence of a Decrease in CD4 Recovery Once Back on Antiretroviral Therapy After Sequential ≥6 Weeks Antiretroviral Therapy Interruptions

To the Editor:

The implementation of short-term (less than 12 weeks) interruptions of suppressive antiretroviral therapy (ART)[1] is not uncommon in clinical management of HIV infection. Studies to date on planned, supervised, short-term ART interruptions (TIs) have shown that although sequential TIs do not result in decreased levels of viral rebound, they also do not seem to have a negative impact on the return of $CD4^+$ T-cell count to preinterruption levels once ART is reinitiated and viral resuppression achieved. We have revisited this finding by assessing changes in $CD4^+$ and $CD8^+$ T-cell count in chronically suppressed HIV-1–infected subjects after a maximum of 8 sequential TIs and ART-mediated viral suppression.

Our study cohort comprised of 21 chronically suppressed HIV-1–infected subjects participating in 2 sequential studies based in Philadelphia: (*a*) an initial study of chronically suppressed HIV^+ patients randomized to a maximum of 4 sequential TIs (2, 4, and 6 weeks and a final open-ended TI) (results from this study are described in PLoS medicine[2]) and (*b*) an observational study of 13 of the 21 subjects from the initial study, undergoing a maximum of 4 additional TIs (3 TIs of 6 weeks each and 1 open-ended TI). Recruitment characteristics were age ≥18 years, on ART (≥3 drugs), CD4 count >400 cells per microliter at entry with a history of nadir CD4 ≥100 cells per microliter, and plasma HIV-1 RNA (viral load) <50 copies per milliliter at entry with >6 months history of <500 copies per milliliter as described.[2] For analysis purposes, 2 groups were used as follows: (*a*) group 1 (n = 21): patients with number of TIs varying from 1 to 8 and (*b*) group 2 (n = 11): patients undergoing all 8 TIs. All ART interruptions were followed by resumption of ART and resuppression to plasma HIV-1 RNA <50 copies per milliliter before any subsequent TI. Clinical parameters (viral load and $CD4^+$ and $CD8^+$ T-cell count) were measured by Quest Diagnostics (Horsham, PA) every 4 weeks on ART and every 2 weeks during TIs. All subjects were recruited and followed at the Jonathan Lax Immune Disorder Clinic in Philadelphia. Informed consent was obtained from all patients in this study, and human experimentation guidelines of the US Department of Health and Human Services and of the authors' institutions were followed. Statistic analysis and modeling were performed using *R*, version 2.6.2.

Patients (n = 21) were followed for an average of 1079 days (standard error [STE] = 113.25 days). As expected, comparison of $CD4^+$ and $CD8^+$ T-cell count at beginning and end of each TI showed a decrease in $CD4^+$ T-cell count when viral rebound was present (data not shown). To further assess how the $CD4^+$ and $CD8^+$ T-cell count change over time as a result of multiple sequential TIs, mixed effect models were applied using the $CD4^+$ and $CD8^+$ T-cell count at the start of each TI when ART-mediated viral resuppression to plasma HIV-1 RNA <50 copies per milliliter was achieved ("TI baseline" values). The variation in measurement of $CD4^+$ and $CD8^+$ T-cell count that could be associated with the method used was also accounted in this model. Initial results for changes in TI baseline $CD4^+$ T-cell count over time showed a significant 18.9% decrease from 683.91 cells per cubic millimeter (first starting mean $CD4^+$ T-cell count baseline on ART) to 554.63 cells per cubic millimeter (last mean $CD4^+$ T-cell count baseline on ART) over the entire period of 8 TIs (n = 11, $P = 0.001$). In further defining whether the decrease observed was equal across all TIs, an inflection point was applied to the model (Fig. 1). A significant change was not detected in TI baseline $CD4^+$ T-cell levels for any of the groups during the first 4 TIs, though the point estimate for the slope was negative for group 2 (n = 11). In contrast, a significant trend of decrease in TI baseline $CD4^+$ T-cell count was observed for both groups (n = 21, $P = 0.029$; n = 11, $P = 0.024$) after the fourth TI, which was also the first TI with duration longer than 6 weeks. Interestingly, no change was found in TI baseline $CD8^+$ T-cell count on ART over the entire period of 8 TIs.

Conclusions of a decreased recovery of $CD4^+$ T cells after ART reinitiation and viral suppression after each TI were also supported by 2 time point comparisons, using Wilcoxon signed rank tests, of $CD4^+$ and $CD8^+$ T-cell count at study entry and at baseline of each sequential ART interruption. Results showed a significant decrease in $CD4^+$ T-cell count after the seventh (group 1: $P = 0.042$; group 2: $P = 0.019$) and eighth (group 1: $P = 0.007$; group 2: $P = 0.007$) interruption of ART. As observed before, no change was observed on $CD8^+$ T-cell count at these time points for any of the analysis groups.

We now provide the first evidence of a potential "cost" of repeated TIs with duration ≥6 weeks on $CD4^+$ T-cell count after reinitiation of the same ART regimen and achievement of viral suppression to <50 copies per milliliter. Although observations by us and others[2–7] do not support an immediate immunological "cost" of short-term TIs (<6 weeks) on $CD4^+$ T-cell count, our present findings now define a potential incremental 2%–3% "cost" in recovery of $CD4^+$ T-cell count on ART after each TI of ≥6 weeks. Although therapy interruptions for clinical management purposes or due to other causes (therapy supply lapses in resource-limited settings) are likely to continue to occur, our data now shows that ≥6 weeks viral replication can have a limited but negative impact on the degree of recovery of immune reconstitution after ART reinitiation. However, it is also acknowledged that our data also reconfirms that short-term TIs are unlikely

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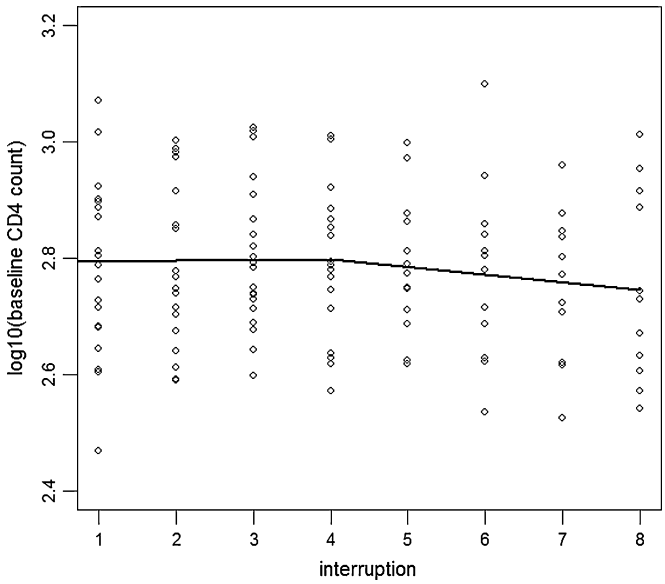

FIGURE 1. The CD4⁺ T-cell count over sequential therapy interruptions. Shown is estimated $\log_{10}$ baseline CD4⁺ T-cell count for the group of 21 HIV-1–infected patients based on mixed effect model. The model is fitted with 2 slopes, with 1 inflection point at the fourth interruption. The random effects include the intercept and the first slope.

to affect immune reconstitution once on ART and that the limited impact on CD4 recovery, documented here for longer TIs, would not represent a major criteria by itself preventing a longer TI from being considered, if clinically warranted.

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REFERENCES

1. Azzoni L, Papasavvas E, Montaner LJ. Lessons learned from HIV treatment interruption: safety, correlates of immune control, and drug sparing. *Curr HIV Res*. 2003;1:329–342.
2. Papasavvas E, Kostman JR, Mounzer K, et al. Randomized, controlled trial of therapy interruption in chronic HIV-1 infection. *PLoS Med*. 2004;1(3):e64.
3. Dybul M, Chun TW, Yoder C, et al. Short-cycle structured intermittent treatment of chronic HIV infection with highly active antiretroviral therapy: effects on virologic, immunologic, and toxicity parameters. *Proc Natl Acad Sci U S A*. 2001;98:15161–15166.
4. Dybul M, Nies-Kraske E, Daucher M, et al. Long-cycle structured intermittent versus continuous highly active antiretroviral therapy for the treatment of chronic infection with human immunodeficiency virus: effects on drug toxicity and on immunologic and virologic parameters. *J Infect Dis*. 2003;188: 388–396.
5. Martinez-Picado J, Frost SD, Izquierdo N, et al. Viral evolution during structured treatment interruptions in chronically human immunodeficiency virus-infected Individuals. *J Virol*. 2002;76:12344–12348.
6. Ortiz GM, Wellons M, Brancato J, et al. Structured antiretroviral treatment interruptions in chronically HIV-1-infected subjects. *Proc Natl Acad Sci U S A*. 2001;98: 13288–13293.
7. Oxenius A, Price DA, Gunthard HF, et al. Stimulation of HIV-specific cellular immunity by structured treatment interruption fails to enhance viral control in chronic HIV infection. *Proc Natl Acad Sci U S A*. 2002;99: 13747–13752.

A Randomized, Open-Label Study of a Nucleoside Analogue Reverse Transcriptase Inhibitor–Sparing Regimen in Antiretroviral-Naive HIV-Infected Patients

To the Editor:

A decrease in ratio of mitochondrial DNA to nuclear DNA (mtDNA:nDNA), a possible marker of mitochondrial toxicity, might be expected with nucleoside analogue reverse transcriptase inhibitors (NRTIs) but not with NRTI-sparing regimens.[1–3] The dyslipidemic effects of lopinavir/ritonavir (LPV/r)[4,5] might be counteracted by the beneficial effects of nevirapine (NVP),[6,7] making this a potentially attractive NRTI-sparing option. The objective of this study was to compare NVP/LPV/r with 2 NRTI-based regimens, zidovudine/lamivudine (ZDV/3TC) plus either NVP or LPV/r, with respect to 48-week changes in mtDNA:nDNA ratio and with respect to efficacy, safety, and changes in metabolic parameters over 48 and 96 weeks.

The study enrolled medically stable antiretroviral-naive HIV-infected adults with HIV RNA >5000 copies per milliliter, with no upper CD4 limit for either gender, as enrollment in this study predated the CD4 threshold recommendations for starting NVP.[8] The study protocol and subject informed consent form were approved by the Research Ethics Boards of the participating institutions. Eligible patients were randomized equally to 1 of the 3 treatment arms: LPV/r 533/133 mg [4 Kaletra capsules (Abbott Laboratories, North Chicago, IL)] twice daily plus NVP 200 mg [1 Viramune tablet (Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT)] twice daily; ZDV/3TC 300/150 mg [1 Combivir film–coated tablet (GlaxoSmithKline, Research

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Triangle Park, NC)] twice daily plus NVP 200 mg twice daily; ZDV/3TC 300/150 mg twice daily plus LPV/r 400/100 mg (3 Kaletra capsules) twice daily. Randomization was stratified by country (Canada, France, Spain, Argentina) using variable block sizes of 3 and 6. Patients allocated to either of the 2 NVP-containing regimens received 200 mg daily for the first 14 days. The LPV/r dose was adjusted upwards in the LPV/r/NVP arm, based on the pharmacokinetic interaction between these agents.[9] Patients were evaluated at regular intervals over 96 weeks for complete blood cell counts, chemistry including liver enzymes, lactate, fasting glucose and lipids, CD4 cell count, and plasma HIV RNA (Roche Amplicor assay version 1.5). Venous whole blood was shipped to the British Columbia Centre for Excellence in HIV/AIDS Laboratory in Vancouver, Canada, where the relative ratio of mtDNA:nDNA was determined by a semi-quantitative real-time polymerase chain reaction–based assay as described previously.[2,3] Continuous variables were compared between groups using the Kruskal–Wallis and Wilcoxon rank sum tests for 3-group and 2-group comparisons, respectively. Categorical variables were compared using χ^2 or Fisher exact test, as appropriate. Safety analysis included all randomized subjects who took at least 1 dose of study drug.

Between February 3, 2003, and July 8, 2004, 77 subjects were enrolled. Baseline characteristics were similar for the 3 treatment groups for the whole study and for the patients in the mtDNA:nDNA analysis. Overall, 75% of study participants were male, median age was 37 years [interquartile range (IQR) 33–42], 58% had HIV RNA >75,000 copies per milliliter, median CD4 cell count was 210 cells per cubic millimeter (IQR 130–271), median CD4 fraction was 16% (IQR 10–20), and median mtDNA:nDNA ratio was 1.93 (IQR: 1.70–2.08). mtDNA:nDNA and efficacy results for the 3 groups are shown in Table 1. Among 26 unselected patients with available whole blood samples, mtDNA:nDNA ratios did not change significantly between baseline and 48 weeks in any treatment arm. In the 2-way comparison of the NRTI-sparing vs. NRTI-containing regimens, mtDNA:nDNA decreased by a median of 3% (IQR −19 to 3) for LPV/r/NVP (n = 7) compared with a median increase of 11% (IQR −5 to 24) for the ZDV/3TC arms combined (n = 19; $P = 0.16$). Grade 3 or grade 4 adverse events leading to permanent discontinuation of 1 or more study drugs were predominantly observed in the LPV/r/NVP arm, occurring in 9 of 26 patients in this arm (5 rash, 4 transaminitis), as compared with 2 of 26 patients in the NVP/ZDV/3TC arm (both rashes) and 0/25 in the LPV/r/ZDV/3TC arm. Grade 3 or grade 4 adverse events were frequently observed in women receiving NVP: 3 of 6 women randomized to LPV/r/NVP (3 rashes, 1 with transaminitis), 2 of 10 women randomized to NVP/ZDV/3TC (2 rashes), as compared with none of the 3 women randomized to LPV/r/ZDV/3TC. Two of the 5 women who experienced rash with or without liver enzyme elevations while taking NVP had CD4 cell counts above 250 cells per cubic millimeter at the time of starting NVP. Changes in lipids and lactate from baseline to week 48 are shown in Table 1. Similar trends were observed in the lipid changes between baseline and week 96, with the differences between groups with respect to changes in high-density lipoprotein cholesterol (HDL), ratio of total cholesterol to HDL, and triglycerides remaining statistically significant, although the numbers of subjects are smaller. No differences were observed between arms with respect to changes in low-density lipoprotein cholesterol or glucose from baseline to either week 48 or 96 ($P > 0.2$). Lactate increased in the arms containing ZDV/3TC and decreased in the NRTI-sparing arm at week 48; however, these differences were likely too small to be clinically relevant and were not sustained to week 96 ($P > 0.2$).

In our study among antiretroviral-naive adults, the NRTI-sparing regimen of LPV/r/NVP did not demonstrate any advantages over the ZDV/3TC–containing regimens in terms of effects on mtDNA:nDNA ratios in peripheral

TABLE 1. Results by Treatment Arm

	LPV/r/NVP	NVP/ZDV/3TC	LPV/r/ZDV/3TC	*P*
n randomized	26	26	25	—
n with mtDNA:nDNA	7	9	10	—
mtDNA:nDNA change from 0 to 48 weeks*	−0.06 (−0.36 to 0.10)	−0.08 (−0.12 to 0.3)	+0.26 (0.05–0.34)	0.19
% (n) VL <50, ITT				
48 weeks	42 (11)	50 (13)	68 (17)	0.17
96 weeks	23 (6)	38 (10)	60 (15)	0.03
% (n) VL <50, OT				
48 weeks	73 (11/15)	72 (13/18)	81 (17/21)	0.78
96 weeks	86 (6/7)	83 (10/12)	79 (15/19)	0.99
Median CD4 increase, cells/mm^3				
48 weeks	225	134	190	0.34
96 weeks	243	176	282	0.47
Median changes from baseline to week 48				
TC, mmol/L	+1.8	+0.8	+1.3	0.05
HDL cholesterol, mmol/L	+0.6	+0.4	+0.2	0.01
TC:HDL ratio	−0.8	−1.2	+0.5	<0.01
Triglycerides, mmol/L	+0.4	−0.1	+0.9	<0.01
Lactate, mmol/L	0	+0.2	+0.4	0.03

ITT, intent-to-treat (change in treatment or off study = failure); OT, on treatment; TC, total cholesterol; VL, viral load (copies/mL).
*Median (IQR).

blood; however, these results need to be interpreted with some caution given the limited number of patients included in the analysis. The apparent lack of mitochondrial toxicity with the NRTI-based regimens observed in this study may be due to the selection of ZDV/3TC as the NRTI backbone. Also, study subjects who were not included in the mtDNA analysis, having left the study before 48 weeks due to adverse events, may have shown a greater change in mtDNA:nDNA ratio.

Virologic and immunologic effects were similar for patients who remained on the NRTI-sparing regimen and for those who took either of the 2 ZDV/3TC–based regimens. However, differences were observed in the intent-to-treat analysis: only 6 of 26 patients (23%) randomized to LPV/r/NVP had HIV RNA <50 copies per milliliter by 96 weeks, due to a high dropout rate related to a more frequent occurrence of rash and hepatic adverse events in this arm, especially in women. NVP-related rash and hepatitis were more common with LPV/r/NVP than with NVP/ZDV/3TC, suggesting that LPV/r may potentiate the toxicity of NVP when the 2 are administered together to naive patients; however, the same may not be true for treatment-experienced patients.[10–12] NVP may counteract the adverse impact of LPV/r on lipids: favorable changes in HDL cholesterol and total cholesterol: HDL ratio were seen in both NVP-containing arms. However, based on the findings of our study, the NRTI-sparing regimen of LPV/r/NVP cannot be recommended as first-line therapy in treatment-naive patients.

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REFERENCES

1. Brinkman K, ter Hofstede HJM, Burger DM, et al. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as a common pathway. *AIDS*. 1998;12:1735–1744.
2. Côté HCF, Brumme ZL, Alexander CS, et al. Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. *N Engl J Med*. 2002;346:811–820.
3. Côté HC, Yip B, Asselin JJ, et al. Mitochondrial:nuclear DNA ratios in peripheral blood cells from human immunodeficiency virus (HIV)-infected patients who received selected HIV antiretroviral drug regimens. *J Infect Dis*. 2003;187:1972–1976.
4. Montes ML, Pulido F, Barros C, et al. Lipid disorders in antiretroviral-naïve patients treated with lopinavir/ritonavir-based HAART: frequency, characterization and risk factors. *J Antimicrob Chemother*. 2005;55: 800–804.
5. Oldfield V, Plosker GL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. *Drugs*. 2006;66:1275–1299.
6. Van der Valk M, Kastelein JJP, Murphy RL, et al. Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. *AIDS*. 2001;15: 2407–2414.
7. Clotet B, van der Valk M, Negredo E, et al. Impact of nevirapine on lipid metabolism. *J Acquir Immune Defic Syndr*. 2003;34: S79–S84.
8. Leith J, Piliero P, Storfer S, et al. Appropriate use of nevirapine for long-term therapy. *J Infect Dis*. 2005;192:545–546.
9. Degen O, Kurowsky M, van Lunzen J, et al. Steady state pharmacokinetics (PK) of lopinavir (LPV) in combination with nevirapine (NVP) or efavirenz (EFV) [TuBe4573]. Presented at: XIV International AIDS Conference; July 7–12, 2002; Barcelona, Spain.
10. Negredo E, Molto J, Burger D, et al. Lopinavir/ritonavir plus nevirapine as a nucleoside-sparing approach in antiretroviral-experienced patients (NEKA Study). *J Acquir Immune Defic Syndr*. 2005;38:47–52.
11. Murphy R, Zhang Z, Hafner R, et al. Switching to a thymidine analog-sparing or a nucleoside-sparing regimen improves lipoatrophy: 24-week results of a prospective randomized clinical trial, AACTG 5110 [45LB]. Presented at: 12th Conference on Retroviruses and Opportunistic Infections; February 22–25, 2005; Boston, MA.
12. Benson CA, Deeks S, Brun S, et al. Safety and antiviral activity at 48 weeks of lopinavir/ritonavir plus nevirapine and 2 nucleoside reverse-transcriptase inhibitors in human immunodeficiency virus type 1-infected protease inhibitor-experienced patients. *J Infect Dis*. 2002;185:599–607.

Assessment of Knowledge and Attitudes of Physicians Involved in the Care of HIV-Infected Patients With Respect to Nutrition and Nutritional Supplements

To the Editor:

The use of supplements has been steadily increasing among Canadians and growth seems likely to continue. According to a recent survey by Health Canada in 2005, 7 of 10 Canadians (71%) have ever used a natural health product, and among those, multivitamin/mineral is the major category of supplements used by about 57%. Based on our recent survey,[1] people living with HIV (PLWH) use vitamin/mineral supplements with greater frequency at about 75.6% of patients. However, a study in

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pediatricians suggests that only 25%–30% of physicians ever ask about the use of nutritional supplements as part of the medical history.[2] We were interested to assess the knowledge and attitudes of physicians involved in the care of PLWH with respect to nutrition and use of micronutrient supplements.

An anonymous, self-report, 15-item survey was e-mailed in January 2008 to a sample of 105 Canadian physicians involved in the care of PLWH in the province of Ontario and who were identified by their listing in the directory of The Ontario HIV Treatment Network.

The survey was developed by the authors and based on a survey used in previous studies.[3,4]

The study was approved by the University Health Network Research Ethics Board. Statistical analysis was performed using SPSS software (SPSS version 11.5 Inc, Chicago, IL).

Of 105, 38 (36.2%) physicians responded. All respondents practiced in urban areas, 84% were male, and 86.8% provided care to more than 50 PLWH per year.

Among participants, 50% reported that they had some form of education related to nutrition from postsecondary courses (13.2%), attending conferences and reading medical journals (63.2%), and the internet (31.6%). Based on physician's self-report, perceived nutrition knowledge was high in 5.3%, adequate in 42.1%, and minimal in 56.2%.

Among respondents, 73% were frequently asked by their patients about nutrition and 37% frequently provided advice about it. Although 69.4% of respondents measure body weight routinely, only 32.4% calculate body mass index on a routine basis. Only 2.7% refer patients to a dietician when there is a concern, 27% often refer, and 54.1% sometimes refer for nutritional advice.

Respondents' knowledge was tested by asking basic questions about nutrition and nutritional supplements. The correct response and the percentage of participants who responded correctly are listed in Table 1.

Our results demonstrate that physicians involved in the care of PLWH have suboptimal nutritional knowledge despite the fact that they are often approached by PLWH for advice regarding nutrition and the use of supplements. Use of nutritional supplements is prevalent in PLWH[1] and other adults and children with chronic medical problems.[5,6] However, the data on attitudes and beliefs of physicians involved in the care of PLWH are scant. Our study contributes important information on this issue.

A study in Vietnam[7] reported that 29% of physicians believed that good nutrition can protect people from HIV infection, and 84.3% used nutritional therapies instead of or in conjunction with antiretroviral for PLWH. Similar data are not available for Western countries. A US study[8] recommended that clinic staff regularly measure body mass index in PLWH and use this index to determine whether dietitian referral is appropriate. They recommended that clinics promote good nutrition and that they hire a 0.4 full-time equivalent dietician.

Several studies assessing attitudes, beliefs, and use of alternative therapies by primary care physicians in the United States, Canada, and Europe reported that 10%–80% of physicians expressed an interest in complementary/alternative treatments, wanted more education, had a positive attitude toward these treatments, and considered referring patients to complementary care practitioners.[9–11] Kemper and O'Connor[2] also found that 87% of pediatricians were asked about complementary/alternative treatments by their patients; by contrast, the pediatricians did not feel comfortable discussing or recommending these therapies, and less than a quarter of these physicians were asking about these treatments, as part of the medical history.[2] Physicians' skepticism and lack of knowledge and training about complementary/alternative treatments might be driving this trend. A study by Wetzel et al[12] of 117 medical schools in the United States found that 64% of the medical schools stated they offered either an elective in complementary/alternative treatments or the topic of alternative medicine was included into a required course, but there was great diversity in the content and format among these courses.

In summary, physicians caring for PLWH have a suboptimal level of knowledge with respect to nutrition and nutritional supplements. One point that should be kept in mind is that the majority of physicians listed in the directory of the Ontario HIV Treatment Network practice in urban areas and in academic hospitals in Ontario. Therefore, they may have had more exposure to educational sessions and thus these results may in fact underestimate the prevalence of suboptimal knowledge among the physicians involved in the care of PLWH in the community.

Given the potential toxicity from micronutrient overdose and their interactions with the antiretroviral medications, physicians involved in the care

TABLE 1. Respondents' Knowledge About Nutrition and Nutritional Supplements

	Correct Answer (% of Respondents)	Did Not Answer (% of Respondents)
What is the formula for calculation of BMI?	wt (kg)/height (m^2) (50)	21.1
What is the normal range for BMI?	20–25 kg/m^2 (71.7)	7.9
What is the recommended % energy intake from dietary fat?	<30% (47.4)	7.9
If a label on a cod liver oil supplement bottle states maximum dose is 3 times per day but the patient believes that if some is good, more is better and takes 6 capsules/day, which vitamin toxicity would you be concerned with?	Vitamin A (34.2)	23.7
Which one of the following is an antioxidant?		
Riboflavin	No (83.3)	0
Vitamin D	No (91.7)	0
Selenium	Yes (41.7)	0
Calcium	No (97.2)	0
Vitamin E	Yes (86.1)	0
Chromium	No (83.3)	0
Beta carotene	Yes (77.8)	7.9
Vitamin C	Yes (69.4)	0

BMI, body mass index.

of PLWH need to be more aware of this issues and should be more educated with respect to nutrition and nutritional supplements.

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REFERENCES

1. Aghdassi E, Bondar H, Salit IE, et al. Nutritional and nutritional supplements: knowledge and attitudes of HIV-positive patients. Presented at: European Society for Clinical Nutrition and Metabolism; 2008; Florence, Italy.
2. Kemper KJ, O'Connor KG. Pediatricians' Recommendations for Complementary and Alternative Medical (CAM) Therapies. *Ambul Pediatr*. 2004;4:482–487.
3. Sawni A, Thomas R. Pediatricians' attitudes, experience and referral patterns regarding complementary/alternative medicine: a national survey. *BMC Complement Altern Med*. 2007; 7:18.
4. Sikand A, Laken M. Pediatricians' experience with and attitudes toward complementary/ alternative medicine. *Arch Pediatr Adolesc Med*. 1998;152:1059–1064.
5. Barnes PM, Powell-Griner K, McFann K, et al. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data*. 2004;343:1–19.
6. Sawyer MG, Gannoni AF, Toogood IR, et al. The use of alternative therapies by children with cancer. *Med J Aust*. 1994;160: 320–322.
7. Quach L, Mayer K, McGarvey ST, et al. Knowledge, attitudes, and practices among physicians on HIV/AIDS in Quang Ninh, Vietnam. *AIDS Patient Care STDS*. 2005;19: 335–346.
8. Sharkey SJ. An assessment of the need for a dietitian in an out-patient HIV clinic. *J Can Diet Assoc*. 1993;54:202–207.
9. Berman BM, Singh BB, Hartnoll SM, et al. Primary care physicians and complementary-alternative medicine: training, attitudes and practice patterns. *J Am Board Fam Pract*. 1998; 11:272–281.
10. Ernst E, Resch K-L, White AR. Complementary medicine. What physicians think of it: a meta-analysis. *Arch Intern Med*. 1995;155: 2405–2408.
11. Levine SM, Weber-Levine M, Mayberry RM. Complementary and alternative medical practices: training, experience and attitudes of a primary care medical school faculty. *J Am Board Fam Pract*. 2003;16:318–326.
12. Wetzel MS, Eisenberg DM, Kaptchuk TJ. Courses involving complementary and alternative medicine at US medical schools. *JAMA*. 1998;280:784–787.

Lack of Significant Cross-Reactivity for HIV-2 Immunoblots in HIV-1–Infected Patients

To the Editor:

In a recent report, McKellar et al[1] found a high rate of false positive results for HIV-2 infection in a cohort of HIV-1 long-term nonprogressors (LTNP) (3/13) using a specific HIV-2 immunoblot test. The authors concluded that because of cross-reactivity with HIV-1, serologic testing for HIV-2 should only be used in patients with negative HIV-1 Western blot (WB) results, at least in HIV-2 nonendemic areas. Their recommendation would be to perform directly HIV-2 polymerase chain reaction (PCR) testing in subjects in whom this infection is suspected.

We want to communicate our experience that is quite different from the one reported by McKellar et al.[1] At our institution in Madrid, which includes a Tropical Medicine Unit, HIV-2 is screened in a routine basis in all HIV-seropositive individuals. Samples with reactivity in an HIV-1/2 enzyme immunoassay (EIA) are confirmed using an HIV-1 WB and a commercial line peptide assay (LIA) (Pepti-Lav; Bio-Rad, Marnes la Coquette, France). The latest is a synthetic peptide-based assay that contains both transmembrane proteins gp41 of HIV-1 and gp36 of HIV-2. Only in subjects with reactivity to both bands, HIV-2 WB and/or specific HIV-2 PCR are performed to definitively confirm HIV-2 infection.

We retrospectively reviewed HIV testing results obtained from January 2005 to December 2007. A total of 563 subjects were found to be reactive in an HIV-1/2 EIA. Of them, 435 were Spaniards and 128 were immigrants, mainly from West Africa, where HIV-2 is endemic. The final report for this population of HIV-infected subjects was as follows: 497 HIV-1 positive, 4 HIV-2 positive, 1 dually infected by HIV-1 and HIV-2, and 61 HIV negative. HIV-2 was excluded or confirmed using a validated HIV-2 PCR test. Interestingly, of the 497 HIV-1–positive patients, only in 31 (6.2%) subjects the HIV-2 gp36 band in the LIA was reactive. However, in all these cases the gp36 band reactivity was weak. No relationship between the geographical origin of the patients and recognition of serological cross-reactivity was found. Finally, we investigated cross-reactivity using the LIA in a well-characterized cohort of HIV-1–infected LTNP, already described elsewhere.[2] Of 20 individuals examined, none of them showed reactivity to the HIV-2 gp36 band.

Our results support that serological cross-reactivity for HIV-2 infection using synthetic peptide-based assays in HIV-1–infected patients is uncommon. This is not surprising because the *env* genes in gp41 HIV-1 group M and gp36 for HIV-2 regions show up to a 50% divergence in their amino acid sequences. The findings of McKellar may be explained by the degree of cross-reactivity in some immunoblot assays, in which a recombinant HIV-2 protein is used.[3] Synthetic peptides of specific antigenic regions may be more specific. Furthermore, the authors carried out the exam of a group of LTNP, who characteristically present a broader antibody response[4] and therefore could have a higher tendency to cross-react. Using the synthetic peptide assay, we did not find any cross-reactivity in our cohort of LTNP.

Finally, in agreement with McKellar et al,[1] we found that reactivity to the gp36 band in the immunoblot is generally weak when present in HIV-1–infected persons. To exclude cross-reactivity, performance of serial dilutions using synthetic peptide-based assays can resolve the dual seroreactivity.[5] Binding is stronger and only remains for specific either HIV-1 or HIV-2 antibodies.

In summary, although HIV-2 infection is relatively uncommon outside endemic regions, international travel and immigration may support to implement diagnostic strategies to discharge HIV-2 infection. Synthetic peptide-based assays are commercially available, easy to perform and relatively cheap, and may be helpful to exclude HIV-2 in initially HIV-1/2 EIA-reactive samples.

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REFERENCES

1. McKellar MS, Jongthavorn P, Khanlou H. False-positivity of HIV-2 immunoblots in a cohort of elite suppressors infected with HIV-1. *J Acquir Immune Defic Syndr*. 2008;47:644.
2. Rodés B, Toro C, Paxinos E, et al. Differences in disease progression in a cohort of long-term non-progressors after more than 16 years of HIV-1 infection. *AIDS*. 2004;18:1109–1116.
3. Andersson S, da Silva Z, Norrgren H, et al. Field evaluation of alternative testing strategies for diagnosis and differentiation of HIV-1 and HIV-2 infections in an HIV-1 and HIV-2-prevalent area. *AIDS*. 1997;11:1815–1822.
4. Cao Y, Qin L, Zhang L, et al. Virologic and immunologic characterization of long-term survivors of human immunodeficiency virus type 1 infection. *N Engl J Med*. 1995;332:201–208.
5. Soriano V, Gutiérrez M, Heredia A, et al. Serial dilutions on synthetic peptide-based assays can resolve dual seroreactivity to HIV-1 and HIV-2. *Vox Sang*. 1996;71:67–68.

A Brazilian Experience in Response to "Optimum Time to Initiate Antiretroviral Therapy in Patients With HIV-Associated Tuberculosis"

To the Editor:

We were very interested on the discussion of Drs Lawn and Wood with Drs Schiffer and Sterling[1,2] about the optimal timing to initiate antiretroviral (ARV) therapy in patients with HIV-associated tuberculosis (TB). In our opinion, no consensus exists yet, neither in the developed world nor in resource-poor countries. Currently, we are confronting different data from patients living in developed world[3,4] on the one hand and from the African population[5] on the other.

Brazil has an intermediate situation considering all problems pointed in this discussion. We are a country with a high TB burden, and we have a national program with free access to patients with HIV/AIDS; what makes easier for health care workers to treat HIV-associated TB, although the question about the best moment to initiate ARV remains unclear.

In our center, the standard of care is to initiate ARV therapy 4 weeks after TB treatment (including rifampicin in the first-line regimen). This strategy was based on rifampicin metabolism and steady state[6]; the greater incidence of adverse events during the first 15 days of anti-TB drugs,[7] which sometimes require drug discontinuation and reinstitution; and on the fact that most TB-related deaths observed in our cohort occurred during the first 3 months of TB therapy.

Frequently in Brazil, patients diagnosed with TB arrive at the research sites after seeking medical care in primary health care units, most of these with limited resources to diagnose TB in patients with AIDS. Therefore, most of them presented clinical signs and symptoms during 2 or 3 months before TB diagnosis and treatment initiation. This information is very important to be taken into account to make a decision about ARV therapy. Most of these patients die soon after starting TB treatment, and sometimes they even had the chance to get highly active antiretroviral therapy (HAART).

We treated patients with HIV with culture-documented TB from January 2000 to August 2006 with rifampicin as part of TB therapy in 82% of the patients. We had 19.8% TB-related deaths during the study, half of them (10 deaths—9.4%) occurring within the first 3 months after TB diagnosis. Use of HAART during TB treatment was associated with a significant reduction in TB-related mortality.

Conversely, paradoxical reaction is a little less frequent (6.6%) among our patients than reported elsewhere.[5,8] Although we use this strategy of initiating HAART at least 4 weeks after TB therapy, we did not observe a higher incidence of immune reconstitution disease (IRD). We are very aware of the signs of IRD, and we treat IRD with prednisone 1 mg/kg with a very good response. We have never observed a death related to IRD, therefore, we do not feel it is required to delay ARV initiation. Instead of delaying ARV initiation after pirazinamide discontinuation due to the risk of adverse events, we are much more afraid of the effect of delaying AIDS therapy too long.

In conclusion, although many factors should be taken into account to make a decision on ARV therapy in patients with TB, we believe that this Brazilian data could offer new results to be considered on this discussion.

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REFERENCES

1. Lawn SD, Wood R. Optimum time to initiate antiretroviral therapy in patients with HIV-associated tuberculosis. There may be more than one right answer. *J Acquir Immune Defic Syndr*. 2007;46:121–123.
2. Schiffer JT, Sterling TR. Response to "optimum time to initiate antiretroviral therapy in patients with HIV-associated tuberculosis. There may be more than one right answer." *J Acquir Immune Defic Syndr*. 2007;46:122–123.
3. Lawn SD, Myer L, Bekker LG. et al. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. *AIDS*. 2006;20:1605–1612.
4. Lawn SD, Myer L, Orrell C. et al. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *AIDS*. 2005;19:2141–2148.
5. Schiffer JT, Sterling TR. Timing on antiretroviral therapy initiation in tuberculosis patients with AIDS: a decision analysis. *J Acquir Immune Defic Syndr*. 2007;44:229–234.
6. Burman WJ, Gallicano K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. *Clin Pharmacokinet*. 2001;40:327–341.
7. Pedral-Sampaio DB, Netto EM, Brites C, et al. Treating tuberculosis in AIDS patients: when to start and how long to keep giving drugs? *AIDS*. 2002;16:1845.
8. Lawn SD, Myer L, Bekker LG. et al. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS*. 2007;21:335–341.

Response to "A Brazilian Experience in Response to Optimum Time to Initiate Antiretroviral Therapy in Patients With HIV-Associated Tuberculosis"

Response to the Editor:

We thank Drs. Stanis Schmaltz, Santoro Lopes, and Cavalcanti Rolla for sharing their experience caring for tuberculosis (TB)/HIV-coinfected patients in Brazil.[1] Data from a setting with a tuberculosis burden intermediate between that of developed countries (which we used in our decision analysis)[2] and South Africa (which Lawn and Wood reported[3]) can potentially provide important information regarding the optimal timing of highly active antiretroviral therapy (HAART) initiation.

Schmaltz et al[1] report a TB-related mortality rate of 19.8%, which is substantially higher than the rate reported from North America that we used in our analysis.[2] However, their rate is comparable with the 12-month rate reported by Lawn and Wood.[3] For Schmaltz's cohort, it would be important to know the total number of patients, whether the cohort was limited to inpatients, whether all patients received HAART, and for those who did, the timing of HAART initiation in relation to TB treatment. HAART initiation presumably did not occur exactly 4 weeks after TB treatment initiation in all patients. Mortality rates among those who did and did not receive HAART would also be helpful, as would inclusion of the time over which mortality was assessed. Data from Brazil that correspond to the events included in Table 1 of our article could then be used to determine the optimal timing of HAART initiation in the setting of Schmaltz et al.[1]

The low rate of immune reconstitution inflammatory syndrome and low immune reconstitution inflammatory syndrome–related mortality rate reported by Schmaltz et al[1] would tend to favor early HAART initiation. However, as we noted in our response to Lawn and Wood[2], it is important to include probability estimates relevant to a particular setting (eg, Brazil) for all variables in the decision analysis, not just a selected few.

We eagerly await the results of randomized clinical trials to help guide clinical decision making for this complex situation. The largest of the ongoing trials is enrolling subjects from the United States, Brazil, the Congo, India, Malawi, Peru, South Africa, and Thailand.[4] Even if the results of this trial suggest a definitive answer regarding timing of HAART initiation, clinicians will still need to consider whether these results can be generalized to their specific setting and their individual patient. The decision regarding optimal timing of HAART initiation in HIV-infected patients with TB with $CD4^+$ lymphocyte count <200 might therefore still benefit from carefully performed decision analyses based on pertinent local data.

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REFERENCES

1. Schmaltz CA, Lopes GS, Rolla VC. A Brazilian experience in reponse to "optimum time to initiate antiretroviral therapy in patients with HIV-associated tuberculosis." *J Acquir Immune Defic Syndr*. 2008.
2. Schiffer J, Sterling T. Timing of antiretroviral therapy initiation in tuberculosis patients with AIDS: a decision analysis. *J Acquir Immune Defic Syndr*. 2007;44:229–234.
3. Lawn S, Wood R. Optimum time to initiate antiretroviral therapy in patients with HIV-associated tuberculosis: there may be more than one right answer. *J Acquir Immune Defic Syndr*. 2007;46:121–123; author reply 123.
4. Immediate versus deferred start of anti-HIV therapy in HIV infected adults being treated for tuberculosis. Available at: http://clinicaltrials.gov/ct2/show/NCT00108862.

Optimum Time to Initiate Antiretroviral Therapy in Patients With HIV-Associated Tuberculosis: A Reply

To the Editor:

We thank Schmaltz et al[1] for their interest in our article regarding the optimum time to initiate antiretroviral therapy (ART) in patients with tuberculosis (TB). Data from randomized controlled trials that definitively address this question are awaited, but in the interim, data from observational cohorts offer important insights.

The issue of the optimum timing is complex, involving a number of variables including treatment tolerability, cotoxicity, pharmacokinetic drug interactions, and adherence. However, of overriding importance is mortality risk. The 2 key factors contributing to mortality seem to be the mortality risk associated with delays in ART initiation versus the mortality risk associated with immune reconstitution disease (IRD)[2,3]—the latter being strongly associated with early initiation of ART.[4,5] The optimum timing of ART initiation is likely to be defined largely by the balance between these 2 opposing factors. However, both variables seem to vary between different patient populations and, in particular, may differ substantially when comparing treatment cohorts in high-income and low-resource settings.

Mortality risk in the first year of treatment in ART programs in sub-Saharan Africa (8%–26%) greatly exceeds the risk in European and North American cohorts (approximately 2%–3%), with most deaths occurring during the initial months of treatment.[6,7] The mortality cost of delays in ART initiation is therefore likely to be much higher in Africa than in high-income countries. As suggested by Schmaltz et al,[1] an intermediate risk is likely to exist in Brazil.

The reported incidence of TB-associated IRD varies between approximately 10% and 40% of patients with TB initiating ART.[4,8] This wide range may reflect differences in cohort characteristics, timing of ART initiation, and methods of case ascertainment. Recent

publication of consensus case definitions for TB-associated IRD applicable in both high-income and resource-limited settings may help provide standardization and comparability of data.[9]

Mortality risk in patients with TB-associated IRD has yet to be clearly defined. Although the proportion of patients reported to develop TB-associated IRD is generally higher in high-income countries than elsewhere,[8] the associated mortality seems to be low in this setting[4] as is also reported from Brazil.[1,10] In contrast, deaths in patients with TB-associated IRD have been reported in South African and Thai cohorts.[5,11] In South Africa, however, our experience is that severe TB-associated IRD tends to develop in patients who already have high mortality risk, specifically those with the lowest CD4 cell counts and those with disseminated TB. Thus, although 10.5% (2/19) of patients who developed TB-IRD in our cohort died, 9.9% (14/141) of patients with TB who did not develop IRD also died.[5] Thus, development of IRD in this study was not associated with significant excess mortality risk. This observation, however, needs to be clarified in cohorts with larger numbers of cases of TB-associated IRD.

Taking these observations together, we have suggested that the optimum time for ART initiation may differ between settings.[3] We agree with Schmaltz et al[1] that in lower income countries, the risk of mortality associated with delays in ART initiation is likely to substantially outweigh any excess mortality risk from TB-associated IRD. Thus, the optimum timing of ART initiation is likely to be earlier in the course of TB treatment for patients in resource-limited settings compared with those in high-income settings.[2] We agree with current World Health Organization guidelines for low-resource settings that recommend that patients with TB/HIV with CD4 cell counts <200 cells per microliter receive ART within a 2- to 8-week time frame after starting TB treatment but that those with the most advanced immunodeficiency be started as soon as practicably possible.[12] The policy described by Schmaltz et al[1] of starting ART after 4 weeks of TB treatment in Brazil may require some refinement because optimal timing is likely to depend substantially on the patient's current CD4 cell count.

We agree with the further important point made by Schmaltz et al that many patients with TB who require ART experience substantial delays between development of symptoms of TB, establishment of a TB diagnosis, initiation of TB treatment, and subsequent initiation of ART. Thus, although much interest has focussed on the issue of the optimum timing of ART in relation to TB treatment, the potentially more important issue of the overall delays in the care pathway in resource-limited settings have received much less attention. The tools routinely available for diagnosis of TB in HIV-infected patients in the countries with the highest burden of TB are extremely limited, and this contributes substantially to delays. New TB diagnostics with adequate sensitivity and rapidity for use in HIV-infected individuals are urgently required. In South Africa, HIV-infected patients with TB are often referred to ART services only after prolonged delay and yet the mortality associated with even short delays is unacceptably high.[13,14] These health system delays are inherent within overstretched and fragmented primary care services. Well-organized and integrated systems of care for delivery of both TB treatment and ART are urgently needed to reduce these delays and optimize the chance of survival for these patients.

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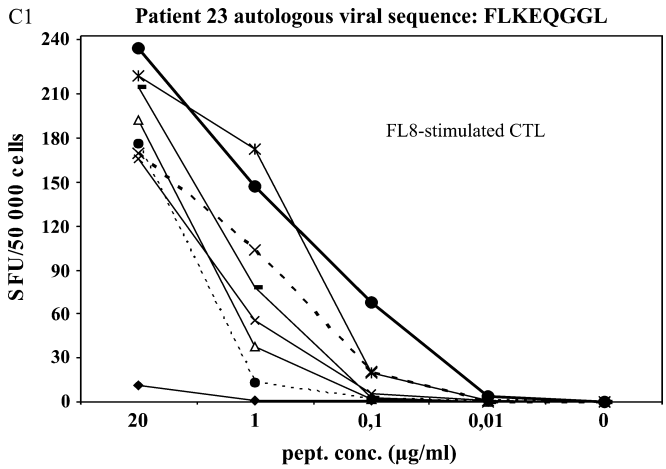
REFERENCES

1. Schmaltz CA, Lopes GS, Rolla VC. A Brazilian experience in response to 'optimum time to initiate antiretroviral therapy in patients with HIV-associated tuberculosis'. *J Acquir Immune Defic Syndr*. 2009;50:340.
2. Schiffer JT, Sterling TR. Timing of antiretroviral therapy initiation in tuberculosis patients with AIDS: a decision analysis. *J Acquir Immune Defic Syndr*. 2007;44:229–234.
3. Lawn SD, Wood R. Optimum time to initiate antiretroviral therapy in patients with HIV-associated tuberculosis: there may be more than one right answer. *J Acquir Immune Defic Syndr*. 2007;46:121–123.
4. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis*. 2005;5:361–373.
5. Lawn SD, Myer L, Bekker LG, et al. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS*. 2007;21:335–341.
6. Lawn SD, Harries AD, Anglaret X, et al. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS*. 2008;22:1897–1908.
7. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet*. 2006;367:817–824.
8. Lawn SD, Lipman MC, Easterbrook PJ. Immune reconstitution disease associated with mycobacterial infections. *Curr Opin HIV AIDS*. 2008;3:425–431.
9. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. 2008;8:516–523.
10. Serra FC, Hadad D, Orofino RL, et al. Immune reconstitution syndrome in patients treated for HIV and tuberculosis in Rio de Janeiro. *Braz J Infect Dis*. 2007;11:462–465.
11. Manosuthi W, Kiertiburanakul S, Phoorisri T, et al. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. *J Infect*. 2006;53:357–363.
12. World Health Organisation. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2006 revision. Available at: http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf. Accessed August 12, 2008.
13. Lawn SD, Myer L, Bekker LG, et al. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. *AIDS*. 2006;20:1605–1612.
14. Lawn SD, Myer L, Orrell C, et al. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *AIDS*. 2005;19:2141–2148.

ERRATA

In the article by Gerber et al, appearing in the *Journal of Acquired Immune Deficiency Syndromes*, Vol. 47, No. 4, pp. 459–466, entitled "Fish Oil and Fenofibrate for the Treatment of Hypertriglyceridemia in HIV-Infected Subjects on Antiretroviral Therapy: Results of ACTG A5186," the description of the immunology assays was incomplete. On p. 464, the Acknowledgments section should include the following: "Immunology assays were performed by Dr. C.R. Rinaldo and staff at University of Pittsburgh, ACTG Immunology Support Laboratory (NIH Grant #U01 AI068636)."

In the article by Maurer et al, appearing in the *Journal of Acquired Immune Deficiency Syndromes*, Vol. 48, No. 2, pp. 133–141, entitled "Role of Cytotoxic T-Lymphocyte—Mediated Immune Selection in a Dominant Human Leukocyte Antigen-B8—Restricted Cytotoxic T-Lymphocyte Epitope Nef," the C1 graph for Figure 3 was incorrect. The newly corrected graph C1 below replaces the previous graph C1 in Figure 3 of the manuscript that was wrongly presenting the graph from patient 20 in B1 instead of the graph from patient 23.



In the article by Luo et al, appearing in the *Journal of Acquired Immune Deficiency Syndromes*, Vol. 50, No. 1, pp. 1–8, entitled "Prevalence of Drug-Resistant HIV-1 in Rural Areas of Hubei Province in the People's Republic of China," the last two column headings of Table 1 are incorrect. The columns which are labeled as "Treated With Detected VL n = 186" and "Treated Without Detectable VL n=102" should instead be labeled "Treated Without Detectable VL n = 186" and "Treated With Detected VL n=102."

This error has been corrected in the online version of the article available at www.jaids.com.

The publisher regrets that this correction was not printed. We apologize for the error.