Interaction Between Atazanavir and Fosamprenavir in the Treatment of HIV-Infected Patients

To the Editor:

Many patients with multidrug-resistant HIV have limited options for salvage antiretroviral therapy. Until new and more potent agents are available, physicians often must design new regimens with current available antiretroviral agents to control HIV viremia and maintain CD4 counts. The use of dual-boosted protease inhibitor (PI)-containing regimens is one option that may offer several benefits.[1] Pharmacokinetic enhancement of 2 different PIs with low-dose ritonavir may result in a higher genetic barrier to resistance and possibly in synergistic activity against HIV. The combination of atazanavir, fosamprenavir, and minidose ritonavir may meet these criteria. Given that fosamprenavir is an inducer of CYP-3A4 metabolism, potential dose alterations and longer follow-up may be warranted.

We examined the trough concentrations (C_{trough}) of atazanavir and fosamprenavir in treatment-experienced patients receiving atazanavir + fosamprenavir + ritonavir who have been intolerant to or have failed lopinavir/ritonavir for a duration of 24 weeks and followed their CD4 and HIV RNA levels. Seventeen patients were selected. Nine patients were given a combination of atazanavir 150/fosamprenavir 700/ritonavir 100 mg twice daily, and 5 patients atazanavir 200/fosamprenavir 700/ritonavir 100 mg twice daily. Three patients did not tolerate ritonavir and were switched to atazanavir 400/fosamprenavir 700 mg twice daily. The $C_{troughs}$ were analyzed using a centralized laboratory with validated techniques (Consolidated Laboratory Services, Van Nuys, CA). The minimum C_{trough} of atazanavir and amprenavir were defined, respectively, as 0.27 μg/mL and 0.28 μg/mL.

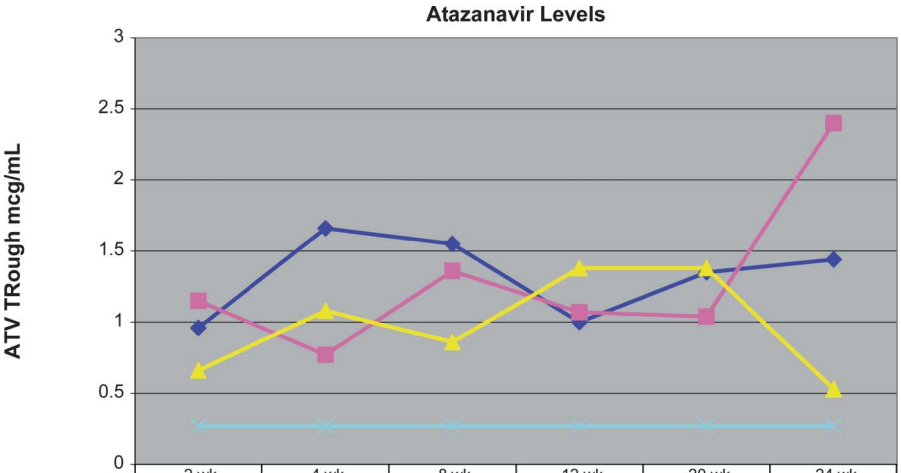
None of the patients were receiving concomitant nonnucleoside reverse transcriptase inhibitors. Nine of 14 patients on boosted regimens (3 on atazanavir 200 mg) were receiving tenofovir 300 mg and emtricitabine 200 mg once daily as part of a nucleoside reverse transcriptase inhibitor backbone, and 2 patients were on fixed-dose zidovudine/lamivudine/abacavir twice daily and 1 was on abacavir + lamivudine twice daily. Two patients were on dual-boosted PIs only (1 with history of lactic acidosis and the other with severe lipoatrophy). The other 3 patients on nonboosted combinations were on abacavir and lamivudine twice daily.

All regimens produced atazanavir and amprenavir C_{trough} well above the minimum acceptable concentrations (Figs. 1 and 2). At 24 weeks, the 3 regimens did improve $CD4^-$ cell count (average: +151 vs. +134 vs. +95 cells/mm^3) and reduce HIV RNA (average: −2.6 vs. −2.11 vs. −3.7 $\log_{10}$, respectively). Overall, at week 24, 10 of 17 patients (60%) achieved HIV RNA levels <400 copies/mL and 4 of 17 (24%) had <50 copies/mL. Interestingly, 2 patients with a very high level of resistance in the protease gene (one with 9 significant mutations including V82A and L90M, and another with 12 significant mutations including I84V and L90M) responded to <50 copies/mL. At 24 weeks, the average total cholesterol levels were 195 vs. 237 vs. 177 mg/dL and triglycerides 210 vs. 196 vs. 177 mg/dL, respectively. One patient on 150 mg/700 mg/100 mg developed grade 3 hyperlipidemia at week 8 and stopped ritonavir with improvement. Four patients did receive concomitant statins.

Overall clinical tolerance was excellent, particularly vis-à-vis the digestive system. However, the occurrence of hyperlipidemia constitutes a limiting factor. In addition, the numbers on a nonritonavir regimen were too small to draw any conclusion, but the lower $C_{troughs}$ are of concern.

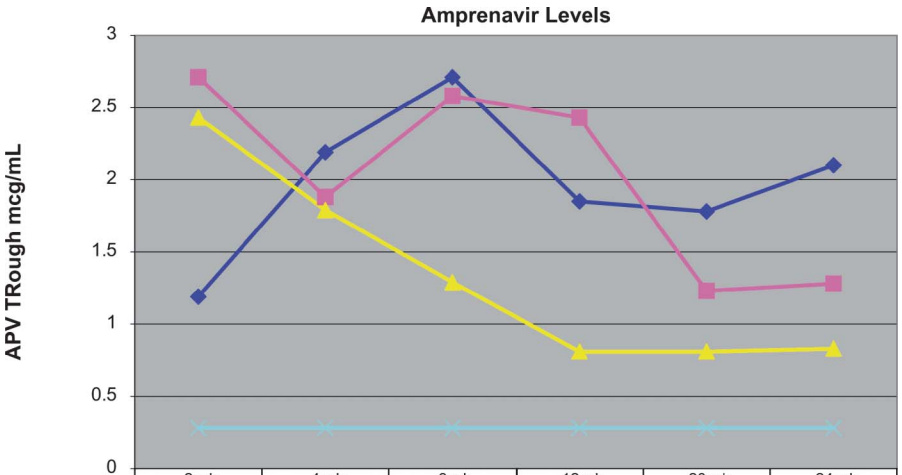
Among different PIs, it appears that combination of atazanavir and fosamprenavir with low-dose ritonavir could offer a great pharmacokinetic advantage, allowing concentrations above the relevant IC_{50} (50% inhibitory concentration) to be achieved safely. This is of importance in the clinical setting, particularly in the presence of multidrug-resistant HIV infection with an increase in the C_{min}:IC_{50} ratio. Previous studies have shown that higher atazanavir C_{trough} levels (ie, 0.774–0.850 μg/mL) were more likely to reduce viral load in experienced patients.[2,3]

However, in the absence of ritonavir inhibition, the C_{trough} of atazanavir was low, requiring administration of an extra dose of atazanavir (400 mg twice daily). The use of therapeutic drug monitoring did allow for adjustment of dosing in patients in whom ritonavir was not used because of patients' preference, intolerability, or history of severe



	2 wk	4 wk	8 wk	12 wk	20 wk	24 wk
150/700/100	0.96	1.66	1.55	1	1.35	1.44
200/700/100	1.15	0.77	1.36	1.07	1.04	2.4
400/700	0.66	1.08	0.86	1.38	1.38	0.53
Min TC	0.27	0.27	0.27	0.27	0.27	0.27

FIGURE 1. Mean atazanavir levels in 3 different regimens.



	2 wk	4 wk	8 wk	12 wk	20 wk	24 wk
150/700/100	1.19	2.19	2.71	1.85	1.78	2.1
200/700/100	2.71	1.88	2.58	2.43	1.23	1.28
400/700	2.43	1.79	1.29	0.81	0.81	0.83
Min TC	0.28	0.28	0.28	0.28	0.28	0.28

FIGURE 2. Mean amprenavir levels in 3 different regimens.

hyperlipidemia. In these patients, although the C_{trough} may have been acceptable for wild-type virus, a dose increase was thought to be necessary.

Another implication of these findings is the importance of therapeutic drug monitoring in the treatment of HIV-infected patients, particularly in those with advanced-stage disease in whom the use of numerous drugs and thus many interactions are expected.

In conclusion, these results appear to indicate that a combination of atazanavir 150 or 200 mg twice daily and fosamprenavir 700 mg twice daily with low-dose ritonavir may offer adequate C_{trough} values for both drugs and may be a viable option for some treatment-experienced patients. Further larger studies evaluating the pharmacokinetics, the effect on P-glycoprotein, and plasma–protein–binding, the virologic efficacy, and the synergism of this combination are perhaps warranted.

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A Series of Skin and Soft Tissue Infections Due to Methicillin-Resistant *Staphylococcus aureus* in HIV-Infected Patients

To the Editor:

Over the past decade, methicillin-resistant *Staphylococcus aureus* (MRSA) infections have been recognized in persons without traditional healthcare-related risk factors[1–4]; these infections are commonly referred to as community-onset or community-acquired MRSA (Ca-MRSA). Skin and soft tissue infections (SSTIs) are most commonly reported.[1,3,4] Unlike most hospital-associated infections, Ca-MRSA is generally susceptible to most non–β-lactam antistaphylococcal antimicrobials.[1,2,5,6]

S. aureus colonizes and infects HIV-infected patients with increased frequency.[7–9] Clonal outbreaks of *S. aureus* infection among hospitalized individuals have occurred.[10,11] Risk factors for *S. aureus* infection in HIV-infected individuals include intravascular catheters, neutropenia, low serum CD4 T-lymphocyte counts, *S. aureus* colonization, and underlying dermatologic conditions.[9,11–13] Reports describe MRSA as an increasingly common cause of SSTIs among HIV-infected patients,[14] including an increase from 1.1 to 3.3/1000 between 1999 and 2001.[15] We describe our experience with HIV-infected patients with Ca-MRSA SSTIs.

Ca-MRSA SSTIs among HIV-infected patients at our institution occurring between June 2003–October 2004 were identified from records of the outpatient infectious disease clinic and inpatient consultation service. Patients were excluded if MRSA was isolated from a source other than skin and soft tissue or was acquired nosocomially. Inpatient and outpatient records were retrospectively reviewed for patient demographics, HIV management and complications, and clinical details of the Ca-MRSA SSTI. The Northwestern Institutional Review Board approved this study.

Results are compiled in Table 1. This case series describes our clinical experience with SSTIs due to MRSA among 11 HIV-infected individuals who did not possess classic risk factors for nosocomial MRSA acquisition. Only 3 patients received antiretrovirals within the preceding 3 months and medication nonadherence was common. Although none of the patients resided in a nursing home, underwent dialysis, or had an intravenous catheter, almost all patients had multiple "healthcare exposures" such as hospitalization or attendance at the HIV outpatient clinic. Prior dermatologic condition or SSTI was noted in more than half, recent antibiotic use was noted in about half, and prior MRSA SSTI was noted in 1 patient. Risk factors for HIV infection were either men who have sex with men or injection drug use. All of these characteristics have been

TABLE 1. Clinical Details of MRSA SSTI in HIV-Infected Patients

	Patient				
	1	**2**	**3**	**4**	**5**
Patient					
Age, Sex	42, Female	46, Male	32, Male	35, Male	40, Female
Ethnicity	AA	AA	AA	White	AA
Characteristics of HIV-Infection					
HIV risk factor	IDU	IDU	MSM	MSM	IDU/HS
Current CD4 (nadir)	8 (8)	338 (287)	7 (7)	673, (160)	6 (6)
History of skin infections	Yes	No	Yes	No	Yes
Prior healthcare	Hospitalized	Clinic	Clinic	Clinic	Hospitalized
Antibiotic exposure in last year	Levofloxacin	None	Levofloxacin Clinda	No	TMP/SMX
Other risk factors for SA infection	PSA, homeless, HIV-induced pruritis	PSA	PSA	Sinusitis	PSA
Clinical information					
Sensitivity pattern*	S-Clinda R-Tetra	S-Clinda S-Tetra	S-Clinda S-Tetra	S-Clinda R-Tetra	S-Clinda S-Tetra
Antibiotic treatment with SA activity	Vancomycin + Proph	Clinda	Clinda + Proph	Clinda	Clinda + Proph
Number of recurrences†	1	0	3	0	0
Sensitivity pattern of recurrent infection	S-Clinda R-Tetra	No recurrence	No culture obtained	No recurrence	No recurrence

	6	**7**	**8**	**9**	**10**	**11**
Patient						
Age, Sex	30, Male	52, Male	46, Male	32, Male	37, Male	37, Male
Ethnicity	White	AA	White	White	AA	White
Characteristics of HIV-Infection						
HIV risk factor	MSM	IDU	MSM	MSM	IDU	IDU/MSM
Current CD4 (nadir)	166 (166)	103 (103)	585 (585)	665 (442)	148 (148)	285 (285)
History of skin infections	No	Yes	No	Yes	No	Yes
Prior healthcare	No	Hospitalized	Clinic	Clinic	Hospitalized	Hospitalized
Antibiotic exposure in last year	No	Linezolid TMP/SMX	No	Amoxicillin-clavulanate	No	Vancomycin β-lactam
Other risk factors for SA infection	PSA	PSA, prior incarceration	Pill esophagitis, laminectomy	PSA	PSA	Surgical repair of perforated gastric ulcer
Clinical Information						
Sensitivity pattern*	S-Clinda S-Tetra	S-Clinda S-Tetra	S-Clinda R-Tetra	S-Clinda R-Tetra	S-Clinda S-Tetra	R-Clinda R-Tetra
Antibiotic treatment with SA activity	Clinda	Clinda	Clinda	Cephalexin	Vancomycin + Proph	Linezolid + ciprofloxacin
Number of recurrences†	0	2	3	1	0	0
Sensitivity pattern of recurrent infection	No recurrence	No culture obtained	R-Clinda R-Tetra	R-Clinda S-Tetra	No recurrence	No recurrence

*D testing not performed. TMP/SMX, linezolid, dalfopristin/quinupristin, fluoroquinolone, and daptomycin sensitivities were not performed. All isolates were susceptible to vancomycin, rifampin, and gentamicin, but resistant to β-lactams and erythromycin.

†Recurrences definition: Any additional documented SSTI (no culture for MRSA was required) occurring in the patient during the study period. None of the recurrent infections occurred at the same site as the prior infection.

AA, African American; Clinda, clindamycin; HS, heterosexual intercourse; I + D, incision and drainage; IDU, injection drug use; MSM, men who have sex with men; Proph, prophylactic medications; R, resistant to; S, sensitive to; Tetra, tetracycline; TMP/SMX, trimethoprim-sulfamethoxazole.

previously described as risk factors for MRSA infection.[5,16,17] Although several studies have shown a correlation between neutropenia or low CD4 T-lymphocyte counts and *S. aureus* colonization or infection,[12,13] this was not readily apparent from our data.

Nine of the 11 patients underwent incision and drainage as part of initial treatment; incision and drainage was less frequently performed with recurrent infection. Other authors have emphasized the importance of incision and drainage, in that when combined with a β-lactam, the procedure was found to constitute sufficient management for some MRSA SSTIs.[17]

Although the spectrum of disease we noted was similar to that of prior Ca-MRSA SSTI reports, a unique feature of our population was the high rate of recurrence. Five of the 11 individuals had >1 SSTI, with 10 total recurrences (range: 1–3). Each recurrence involved a new anatomic location, suggesting MRSA reinfection at a new site. Four recurrences were presumptively treated for MRSA with subsequent symptom resolution. A prior study of HIV-infected individuals reported recurrent *S. aureus* infection complicating *S. aureus* bacteremia.[8] Another report noted recurrence complicating SSTI, endocarditis, and bacteremia, but both nosocomial and Ca-MRSA isolates were involved.[13] To the best of our knowledge, ours is the first

series of Ca-MRSA SSTIs in which a high rate of recurrence has been noted.

In contrast to nosocomial MRSA isolates, which are resistant to most antimicrobial agents, Ca-MRSA isolates often remain susceptible to many antimicrobials.[1,2,5,6] All of our isolates were macrolide resistant and about half were tetracycline resistant; however, almost all isolates remained sensitive to clindamycin, as is typical for Ca-MRSA isolates.[1,2,5,6] Although our laboratory did not initiate routine screening for erythromycin induction of clindamycin resistance by use of a "D test"[6] until after these clinical isolates were obtained, we observed that all patients treated with clindamycin experienced clinical resolution. No deaths occurred as a direct result of MRSA SSTI, although patient 3 died from MRSA bacteremia 3 months after the last SSTI, possibly related to an intravascular catheter. Differences in antibiograms among initial MRSA isolates are not consistent with clonal MRSA spread among the HIV-infected population.

Owing to the retrospective nature of this study, specific details of prior SSTIs and dermatologic diseases were lacking. Risk factors for healthcare-related MRSA acquisition may have been underestimated. Patients received their care from 1 academic center in Chicago that serves primarily HIV-infected persons who are men who have sex with men. Some of the initial reports of Ca-MRSA originated from Chicago,[2,3] but not all regions of the United States have had a similar experience.

Our report constitutes a novel case series of HIV-infected individuals with MRSA SSTI. Physicians should be aware of Ca-MRSA as a potential cause of SSTI in HIV-infected individuals, particularly if they have risk factors. Despite responding well to incision and drainage and antibiotics, recurrences were common. Further epidemiologic data regarding Ca-MRSA infections in HIV-infected patients are needed.

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Patients Experiencing Early Virologic Failure on a Protease Inhibitor- or Nonnucleoside Reverse Transcriptase Inhibitor–Based Initial Regimen Containing a Thymidine Analogue and Lamivudine Can Be Successfully Treated With a Quadruple-Nucleoside Regimen

To the Editor:

The virologic goal of HIV management with antiretroviral therapy (ART) is to achieve durable suppression of HIV-1 RNA to undetectable levels.[1] However, no single ART regimen has been proven to provide life-long viral suppression in all patients. Currently there is not a consensus as to how to treat patients with low-level virologic rebound. A recognized approach has been to allow low-level detectable viremia up to an arbitrary level prior to changing therapy. However, ongoing viral replication in the presence of antiretroviral drugs promotes the selection of drug resistance mutations that may

compromise future treatment options.[2,3] Other approaches include intensifying therapy or changing the entire regimen to include 3 active drugs.[1,4] A single-class compact (3 pills/day) quadruple combination of abacavir (ABC)/lamivudine (3TC)/zidovudine (ZDV) (TZV; Trizivir, GlaxoSmithKline, Research Triangle Park, NC) and tenofovir (TDF; Viread, Gilead Sciences, Foster City, CA) offers an attractive strategy for the treatment of patients experiencing early virologic failure. Quadruple-nucleoside/tide therapy with TZV + TDF has been proven to have similar efficacy and tolerability to nonnucleoside reverse transcriptase inhibitor (NNRTI)-based therapy (3TC/ZDV + efavirenz) in treatment-naive individuals[5] and it may preserve future options in other ART classes.

We conducted ESS30005 to investigate the safety and efficacy of a quadruple-nucleoside/tide therapy (TZV twice daily + TDF once daily) in HIV-1–infected patients experiencing early virologic failure on a thymidine analogue–containing protease inhibitor (PI)- or NNRTI-based regimen. HIV-1–infected adults were eligible for enrollment if they were on an initial ART regimen containing a thymidine analogue (ZDV or stavudine [d4T]) in combination with 3TC and a PI or NNRTI and were experiencing early virologic failure (defined as confirmed HIV-1 RNA between 400–10,000 copies/mL following a reduction to <400 copies/mL). At baseline, all patients substituted TDF for the NNRTI or PI, a thymidine analogue (ZDV) and 3TC were maintained, and ABC was added to the second-line regimen.

Our single-arm, open-label, evaluative study was conducted at 56 sites in the United States, with 23 sites enrolling 51 patients. The study was approved by institutional review boards and all patients provided written informed consent. The target enrollment for this study was 100 patients; however, finding patients experiencing early virologic failure on a regimen that included ZDV or d4T plus 3TC was more difficult than anticipated. The majority of screen failures (76%, 68/89) were due to HIV-1 RNA <400 copies/mL at the screening visit following an elevation >400 copies/mL prior to screen.

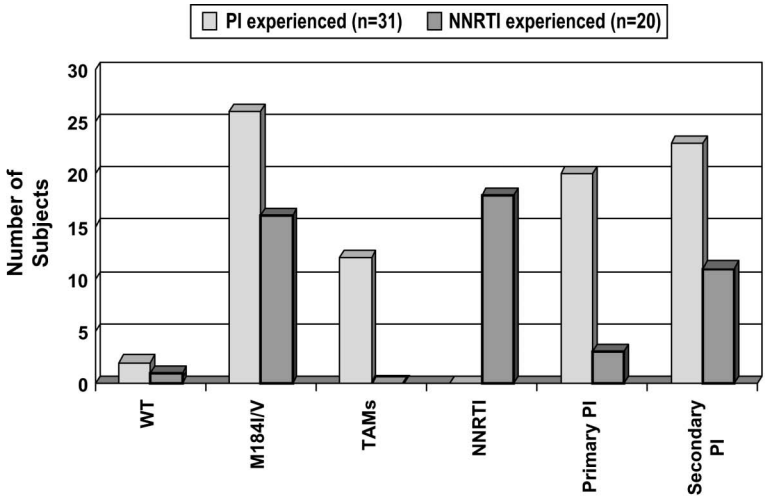
Patients were predominantly male (78%) and nonwhite (61%). Baseline median HIV-1 RNA was 3.295 $\log_{10}$ copies/mL and median CD4 cell count was 436 cells/mm^3. At entry all patients were taking 3TC and either ZDV (61%) or d4T (39%) per protocol requirements; 61% were taking a PI-based regimen, with the remainder taking an NNRTI.

Reasons for premature discontinuation from study were adverse events (4 patients; nausea, fatigue, cancer), lost to follow-up (4), virologic failure (2), protocol violation (2), and site closure (1). The most common drug-related adverse events were nausea (16; 31%), fatigue (12; 24%), headache (4; 8%), vomiting (4; 8%), diarrhea (3; 6%), and insomnia (3; 6%). No drug-related serious adverse events or hypersensitivity reactions to ABC occurred in this ABC-naive population.

Potential patients were excluded if viral genotype at screen indicated >2 NRTI-associated mutations (M41L, A62V, D67N, T69D/S, K70R, L74V/I, V75I, F77L, Y115F, F116Y, Q151M, M184V, L210W, T215Y/F, K219Q/E) or the K65R mutation. Only 1.4% (2/140) of patients screened were excluded owing to genotypic restrictions. At study entry, the majority of patients (80%) had virus containing M184V mutation, as expected in a population exposed to 3TC (Fig. 1). Other common mutational patterns included primary PI mutations (45%) and NNRTI mutations (35%). About ¼ (24%) had a detectable thymidine-associated mutation (TAM), usually in addition to the M184V mutation.

Overall, a high proportion of patients experiencing early virologic failure on an initial ART regimen containing a thymidine analogue, 3TC, and a PI or NNRTI achieved viral suppression with the quadruple-nucleoside regimen of TZV + TDF over 48 weeks (Fig. 2). Similar results were observed in a modified per-protocol analysis, which excluded 4 of 51 patients with HIV-1 RNA <400 copies/mL at baseline. The proportions of patients with HIV-1 RNA <50 copies/mL at week 48 (per protocol analysis) were 75% (27/36, Obs) and 57% (24/47, M = F). Virologic response was also similar between patients with and without TAMs at screen. At week 48, among patients who had TAMs at screen, 7/9 (78%, intention-to-treat, Obs) achieved HIV-1 RNA <50 copies/mL, compared with 23/30 (77%, intention-to-treat, Obs) for those without TAMs at screen. The median CD4 change from baseline at week 48 was an increase of 71 cells/mm^3.

Virologic failure in this study was defined as failure to achieve HIV-1 RNA <400 copies/mL by week 24 or confirmed rebound of HIV-1 RNA ≥1265 copies/mL (0.5-$\log_{10}$ increase over 400 copies/mL) following a reduction to <400 copies/mL. Virologic failure was rare (2/51) despite the presence of M184V or limited TAMs at entry. One patient without resistance mutations at baseline acquired M184V and TAMs (D67N + K70R + K219Q) at the time



TAMS: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E
NNRTI mutations: L100I, K103N, V106M, V108I, Y181C/I, Y188C/L/H, G190A/S, P225H, M230L, P236L
Primary PI mutations: D30N, M46I/L, G48V, I50V, A71V/T, V82A/F/T/S, I84V, L90M
Secondary PI mutations: L10F/I/R/V, K20M/R, L24I, V32I, L33F, M36I, I47V, F53L, I54L/M/V, G73S/A, V77I, N88D/S

FIGURE 1. Genotypic mutations at screen.

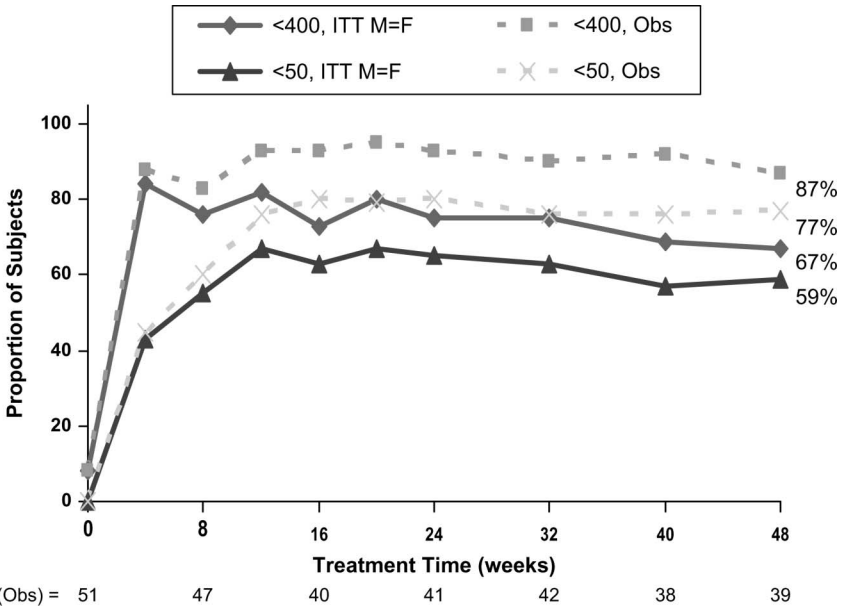


FIGURE 2. Virologic response (HIV-1 RNA <400/HIV-1 RNA <50 copies/mL).

of confirmed virologic failure (week 32). This patient reported incomplete adherence at multiple prior visits. The other patient did not develop treatment-emergent mutations and had evidence of nonadherence. The low rate of virologic failure supports the efficacy of a quadruple-NRTI regimen composed of Trizivir and tenofovir in patients experiencing early virologic failure.

Data from a patient-completed adherence questionnaire suggest that the simplicity of TZV + TDF may have contributed to the virologic efficacy. Of 33 patients with adherence data at week 48, 85% reported perfect adherence over the prior 3 days and prior weekend. The same assessment conducted at baseline revealed that only 68% of these patients were perfectly adherent to their previous failing regimen.

In conclusion, our study demonstrates that patients experiencing early virologic failure on an NNRTI- or PI-based thymidine analogue–containing regimen can be effectively treated with a simple, compact, quadruple regimen of Trizivir and tenofovir even in the presence of M184V and limited TAMs. In the second-line regimen, 3TC and the thymidine analogue were maintained, ABC and tenofovir were added, and the PI or NNRTI from the initial regimen was removed. The quadruple-nucleoside regimen TZV + TDF may help preserve other ART classes for future treatment while offering an effective, tolerable, and simple (3 pills/day) alternative for patients experiencing early virologic failure.

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Association Between Malaria and CD4 Cell Count Decline Among Persons With HIV

To the Editor:

Recent information that episodes of *Plasmodium falciparum* malaria are associated with an average increase of 0.25 log in HIV viral load for approximately 2 months[1] supports previous findings of an association between malaria and viral load.[2] It is not known whether this level and duration of increase in viral load affect HIV disease progression,[3] however, because CD4 cell count measurements, markers of HIV disease progression, were not conducted at follow-up.

To examine the potential long-term effects of clinical malaria on HIV disease, we examined data collected during a 2-year cohort study in Uganda.[4,5] Participants with HIV infection provided blood for CD4 cell count testing at baseline, at 5 months just before they began cotrimoxazole prophylaxis, and 1.5 years later. Participants were visited at their homes weekly. If they reported fever, we took a blood smear, and if the smear was positive for malaria, we brought treatment to the participant's home within 24 hours.

Of 449 HIV-infected persons with available CD4 cell count data for at least

2 time points and no malaria parasitemia at the time of blood draws, baseline CD4 cell counts were <200 cells/μL for 24%, 200 to 500 cells/μL for 45%, and >500 cells/μL for 31%. There were 1024 slides from fever episodes during follow-up, 112 (11%) of which were associated with parasitemia in 92 participants (22.3 episodes of malaria per 100 person-years). The mean time from malaria to the subsequent CD4 cell count was 123 days (range: 7–553 days). Malaria was associated with a more rapid decline in CD4 cell count. Adjusting for sex, age, and baseline CD4 cell count, the mean difference in CD4 cell decline per each additional malaria episode was 40.5 cells/μL per year (95% confidence interval [CI]: 13.1 to 68.0; $P = 0.0038$). Compared with people with no malaria episodes, the mean difference in annual CD4 cell count decline for persons with 1 episode was 5.4 (95% CI: −63 to 74) cells/μL; for persons with 2 episodes, it was 84 (95% CI: 11 to 157) cells/μL; and for persons with ≥3 episodes, it was 142 (95% CI: −26 to 311) cells/μL. The association between malaria and CD4 cell count decline was seen across all baseline CD4 strata ($P = 0.18$ for effect modification of baseline CD4 cell count on the relation between malaria and CD4 cell count decline). Although cotrimoxazole prophylaxis was associated with a decreased incidence of malaria, there was no interaction between prophylaxis, malaria, and CD4 cell count decline.

A possible reason for the association between malaria and CD4 cell count decline could be that people with more advanced disease at baseline were more likely to have malaria during follow-up, because CD4 cell count has previously been associated with incidence of malaria.[6] We controlled for baseline CD4 cell count, however.

In our study, people with malaria were treated promptly; yet, there was still an association with CD4 cell count decline. It may be that the immune reaction to malaria persists beyond the period of acute illness and the 8 to 9 weeks of increased HIV viral load. It would be useful for additional studies to examine the effect of malaria on direct outcomes of HIV disease progression, such as morbidity and mortality. The findings that malaria is associated with increased viral load and a more rapid decrease in CD4 cell count support the importance of malaria prevention among persons with HIV, including the routine use of cotrimoxazole prophylaxis and insecticide-treated bed nets.

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