Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV-1

TO THE EDITOR: I read the recent article by Daar and colleagues (1) with great interest. A portion of the results of this important study has already been published (2), with the more recent results still raising comments and questions.

As written in the article, 2 regimens will be considered equivalent if a 2-sided CI for the hazard ratio (HR) of virologic failure (VF) is entirely within the range of 0.71 to 1.40. The upper boundary of the HR of atazanavir plus ritonavir or efavirenz was 1.56 and 1.46 with abacavir–lamivudine or tenofovir disoproxil fumarate–emtricitabine, respectively.

It seems that the main conclusion of the study is that the results of the trial are inconclusive, and the equivalence could not be demonstrated for the 2 paired comparisons (3). However, the Conclusion section in the abstract indicates that atazanavir plus ritonavir and efavirenz has similar antiviral activity. This could be very confusing after an attempt over several years to provide standardized guidelines, procedures, and design for equivalence and noninferiority trials (3, 4). Although the authors mentioned that criteria for equivalence were not met, a reader could understand that the trial has moved from an equivalence design to an unknown “similarity” design. Table 1 in the article indicates that a larger proportion of patients randomized in the atazanavir plus ritonavir groups were in the high viral load stratum at baseline compared with the efavirenz groups (27.7% vs. 22.5%; P = 0.01). Considering that patients in the high viral load stratum had a higher risk for VF, the unbalanced viral load stratum would favor the efavirenz groups and could explain the slightly higher HR for atazanavir plus ritonavir observed in the article by Daar and colleagues (1). The large difference in the number of patients in the high viral load stratum at screening or baseline was already noted in the previous publication (2). This point is confusing and suggests a post hoc analysis based on the viral load at baseline. As pointed out in the Discussion, at week 96 results showed a lower rate of VF (11% to 17%) than expected (32%). It is not clear how this affects the probability of declaring equivalence because usually larger rates of failure provide larger CIs. In addition, the power of the study is higher than expected, although a 2-sided CI for the hazard ratio (HR) of virologic failure (VF) is entirely within the range of 0.71 to 1.40. The upper boundary of the HR of atazanavir plus ritonavir or efavirenz was 1.56 and 1.46 with abacavir–lamivudine or tenofovir disoproxil fumarate–emtricitabine, respectively.

Loss to follow-up in the A5202 study was high, especially in the efavirenz-based groups, as stated in the note that accompanied the early-release version published on the Annals of Internal Medicine Web site and acknowledged by the authors (1). One third of the patients in the study changed or discontinued the originally allocated regimen. For example, in the efavirenz–abacavir–lamivudine group, only 59% of patients completed follow-up with the assigned regimen, thus resulting in a substantial attrition bias.

For an adequate analysis of noninferiority or equivalence trials, it is imperative to report both on-treatment and intention-to-treat analysis (3, 4). The study did not provide a per-protocol analysis, making it difficult to conclusively state that noninferiority or equivalence was present among the studied interventions. In the context of the aforementioned limitations, the study has limitations in its internal validity; therefore, its results do not provide enough evidence to support the conclusions that atazanavir plus ritonavir and efavirenz provide similar antiviral activity when used with abacavir–lamivudine or tenofovir disoproxil fumarate–emtricitabine.
IN RESPONSE: Dr. Flandre raises important points regarding the ACTG Study A5202 results; however, the abstract’s conclusion does not stand alone. The Results section of the abstract and the Results and Discussion sections of the manuscript state that the equivalence boundary was not met. We do believe that the similarity in response rates is relevant to clinicians considering these treatment options. Differences in baseline HIV-1 RNA values have been addressed in a secondary analysis adjusting for this as continuous and categorical variables (<50 000 copies/mL, 50 000 to <100 000 copies/mL, 100 000 to <500 000 copies/mL, or ≥ 500 000 copies/mL), with the treatment effect estimate showing similar results to the primary analysis. The HRs and 95% CIs when baseline HIV-1 RNA was analyzed as continuous and categorical variables were 1.11 (0.81 to 1.54) and 1.06 (0.77 to 1.47) for abacavir–lamivudine and 1.01 (0.70 to 1.46) and 1.04 (0.72 to 1.51) for tenofovir disoproxil fumarate–emtricitabine, respectively.

Prespecified equivalence boundaries were based on the relative treatment difference of the HR (specified as 0.71 to 1.40). The paper’s Statistical Analysis section states that an HR of 1.40 with a 32% event rate would represent a 96-week difference in probability of VF of approximately 10%. The VF rate makes the current equivalence definition very strict. With the observed rate of approximately 15%, an HR of 1.40 would correspond to an approximately 5% absolute difference, and a 10% difference would correspond to HR boundaries of 0.56 to 1.77.

Dr. Kuchenbecker and colleagues are correct that the drugs compared in this study were open-label; however, blinded protease and nonnucleoside reverse transcriptase inhibitors is challenging and rarely done in recent HIV treatment trials—we acknowledged this in the manuscript as a limitation of the study. We stand by our statement that A5202 was different in design and results from A5142 (1). Unlike the A5142 study, the A5202 study randomly assigned patients to commonly used NRTIs in a blinded fashion and also used atazanavir–ritonavir, which is a preferred agent; this is no longer true for the lopinavir–ritonavir used in A5142 (2). Although the A5202 study was unable to declare equivalence, response rates by all other measures were similar between the 2 regimens. Compared with efavirenz in the A5142 study, the time to VF was significantly shorter with lopinavir–ritonavir (HR, 0.63 [CI 0.45 to 0.87]; P = 0.0006).

We agree with the commentators and acknowledged the relatively high loss to follow-up in the manuscript. We did several sensitivity analyses to address potential attrition bias (Appendix Table 2 in the article), including as-treated analyses in which time to VF failure was censored at modification of the third drug that showed results similar to those of the primary intention-to-treat analysis.

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References

A Transmission Model of the 2010 Cholera Epidemic in Haiti

TO THE EDITOR: The article by Tuite and colleagues (1) proposed a spatially explicit scheme reproducing the sequence and the timing of regional cholera epidemics through waterborne and person-to-person transmission of cholera. Two additional modeling studies of the ongoing Haiti cholera outbreak and its controls were independently and almost simultaneously published (2, 3). In particular, a similar transmission model, based on a finer spatial detail of the affected communities and on alternative descriptions of hydrologic and human mobility drivers of pathogen dispersal (4, 5), has been likewise applied to the unfolding Haiti epidemic (3). Despite differences in the assumptions, the results regarding the effect of control strategies, such as vaccination and sanitation, are similar. However, the article by Bertuzzo and colleagues (3) pointed out that larger intervention efforts involve nontrivial effects, with sanitation exhibiting a threshold-like behavior in effectiveness.

From a modeling standpoint, the main difference between the approaches is that Tuite and colleagues (1) neglect the role of asymptomatic patients who do not report to a hospital, which is suggested to be a critical factor in cholera epidemics, particularly those in Haiti (2, 3). Asymptomatic patients acquire immunity, thus reducing the number of persons in a region who are susceptible to the disease. Figure 4 in Tuite and colleagues’ article shows that their model with realistic values of the basic reproductive number (R0 = 2.78 or 2.90) fits the initial phases of the epidemic but would predict an excessive number of reported cases at later stages. To overcome this, they propose that the effective reproductive number decreases from 3 to
0.5 in the first 3 months of the epidemic, owing to disease-control interventions that would have effectively prevented thousands of cases. A 6-fold decrease of the reproductive number—if asymptomatic patients are not accounted for and the compartment of susceptibles is not depleted—implies a 6-fold decrease of transmission rates.

These figures seem unrealistic, especially compared with the sanitation intervention that Tuite and colleagues analyzed (1): Providing vaccines or clean water to 500,000 persons clearly represents a major effort largely exceeding the disease-control interventions adopted in the first 3 months of cholera insurgence in Haiti, yet it would lead to a much smaller decrease in the transmission rate. This apparent paradox is solved by adopting a model in which asymptomatic infections are accounted for (2, 3). This does not require reproductive numbers to decrease with time because of unspecified disease-control measures to prevent an excess of persons who were calculated to be infected, which is an artifact of neglecting asymptomatic patients (2, 3).

Despite differences in methods, a comparative study on the limits and validity of modeling large-scale epidemic management suggests that such tools should be seen as essential components of future control of cholera epidemics.

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References

IN RESPONSE: We welcome the opportunity to clarify our analysis for Dr. Rinaldo and colleagues. We modeled a pool of infective patients that included both hospitalized and nonhospitalized individuals, but calibrated the model to reproduce hospitalized cases that were accurately measured. Our analysis of vaccines and water was not intended to represent the massive and far more robust multiagency public health response to the Haitian cholera epidemic; rather, it was intended to explore the projected relative effects of low levels of vaccination and water distribution. We did not distinguish symptomatic and asymptomatic cases in our model.

Dr. Rinaldo and colleagues suggest that the marked decline in the rate of growth of Haiti’s cholera epidemic resulted from asymptomatic infection of large numbers of individuals in the population, and that the epidemic effectively stopped by itself. They suggest that our empirical reduction in effective reproductive number (which they misstate as reduction in $R_0$) is problematic and fails to capture the degree to which population immunity resulted in transient control of the epidemic. Recent events in Haiti show this thesis to be implausible, and our modeling approach has unfortunately been somewhat validated by the recent large surge in cholera cases in Haiti since early May 2011. This surge has been particularly marked in the capital region and in the south of the country, as our model projected (1).

It is important to distinguish the basic reproductive number of a disease ($R_0$), which is the average number of secondary cases of infection created by a primary case introduced into a totally susceptible population in the absence of intervention (2), from the effective reproductive number, which is the reproductive number in the presence of immunity or intervention (often denoted $R_e$). Dr. Rinaldo and colleagues confuse these concepts. For $R_0$ to decline from around 3 to around 0.5 solely on the basis of immunity, approximately 85% of the Haitian population would have had to be infected in a 3-month period (2). This would require implausibly short “serial intervals” between cases for a disease with an $R_0$ of 3 (3) and would also have resulted in sufficient herd immunity to make the recent epidemic surge in cholera cases impossible (2). Better data are needed for the modeling and control of cholera in Haiti, but to be credible, modelers need to consider the important and hard-to-measure effects of public health responders in the successful control of epidemics.

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References
Letter

Effect of the Centers for Medicare & Medicaid Services Policy About Deep Sedation on Use of Propofol

TO THE EDITOR: Rex’s article (1) on Medicare policy as it affects use of propofol for procedural sedation confuses the standards set by the Centers for Medicare & Medicaid Services (CMS) for deep sedation. The author, like any physician—anesthesiologist or not—is permitted under Medicare policy to administer deep sedation or general anesthesia if his or her facility has been granted privileges for doing so. The CMS does not forbid gastroenterologists from administering sedatives and anesthesia, but it does forbid them from delegating this responsibility to an endoscopy nurse while occupied with the endoscopy procedure—a policy shared by dozens of state nursing boards. The U.S. Food and Drug Administration’s “black box” warning for propofol forbids its use while performing a procedure, such as endoscopy. This reflects the judgment that the administration of such potent drugs requires the undivided attention of the responsible physician. The Institute for Safe Medication Practices, the American Society of Anesthesiologists (ASA), and other groups take the same view on the hazard of multitasking with deep sedation or anesthesia.

These groups all go further than CMS in stating that because of the unique characteristics of propofol, its use also requires that the user be trained in the administration of anesthesia. The CMS relies on individual institutions under a single anesthesia service to define the qualifications of those given privileges to administer sedation and anesthesia. Rex needs to look no further than oral surgery for an example of a group that has established explicit and uniform training requirements for using anesthesia in a nonanesthesiologist-based practice. The failure of gastroenterology as a specialty to establish such requirements is the real barrier to the acceptance of the practice he proposes.

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Reference


References

OBSERVATIONS

Recurrent Hypomagnesemia With Proton-Pump Inhibitor Rechallenge

Background: Clinicians frequently prescribe proton-pump inhibitors (PPIs) for patients with gastroesophageal reflux disease, gastritis, duodenitis, and peptic ulcer disease without considering the potential for severe side effects. Other observers have reported 4 cases of tetany due to hypocalcemia secondary to hypomagnesemia associated with a PPI (1–3).

Objective: To provide additional support for the association between PPIs and hypomagnesemia.

Case Report: We admitted a 30-year-old woman with Crohn disease whose history included a partial ileal resection and newly detected rectovaginal fistula. Physical examination showed diffuse abdominal tenderness and a blood pressure of 125/80 mm Hg. Blood tests revealed mild hypomagnesemia (magnesium level, 0.63 mmol/L [1.26 mEq/L]) and increase in C-reactive protein level, fibrinogen level, and leukocyte count but none of the sequelae of malabsorption, such as abnormal values for cholinesterase, albumin, or international normalized ratio. We found only mild inflammation confined to the neoterminal ileum during colonoscopy. The patient continued oral treatment with 6-mercaptopurine, mesalazine, calcium carbonate (500 mg/d), and cholecalciferol (1000 IU/d), and we added metronidazole and intravenous corticosteroids. Stool frequency subsequently decreased from 12 to 5 per day.

The patient started treatment of dyspepsia with pantoprazole, 40 mg/d, and 4 days later reported a feeling of pins and needles in her feet and hands that persisted after stopping metronidazole therapy. Ten days later, she reported headaches with numbness and muscle cramping in the right half of the face, right arm, and right leg.

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References
Physical examination showed a hanging right corner of her mouth, a positive Chvostek sign, and elevated blood pressure (140/100 mm Hg). We ruled out a focal neurologic lesion with cerebral computed tomography. Blood tests revealed reduced ionized calcium and magnesium levels (1.89 mmol/L [7.56 mg/dL] and 0.38 mmol/L [0.76 mEq/L], respectively) and levels of parathyroid hormone and cholecalciferol that were within normal ranges (Figure).

The patient was administered intravenous calcium gluconate, which was followed by improvement in her tetany symptoms, but blood pressure remained elevated (155/105 mm Hg). Because gastroscopy revealed *Helicobacter pylori*-positive gastritis, we doubled the dose of pantoprazole and started antibiotic eradication therapy. Low levels of ionized calcium and magnesium persisted in blood and urine samples despite continued intravenous administration of these

**Figure.** Changes in serum levels during treatment with the proton-pump inhibitor pantoprazole.

Top. Serum magnesium levels. Bottom. Serum calcium and magnesium levels and systolic blood pressure. To convert magnesium values to mEq/L, divide by 0.5; to convert calcium values to mg/dL, divide by 0.25. Ca = calcium; IV = intravenous; Mg = magnesium.
minerals, and blood pressure increased to a maximum of 160/100 mm Hg.

When we became aware of reports describing an association between PPIs and hypomagnesemia, we stopped therapy with pantoprazole and replaced it with ranitidine, 150 mg twice daily. The patient’s tetany symptoms and signs resolved within 48 hours. In addition, blood pressure had returned to normal 6 days later, and her ionized serum calcium and magnesium levels had returned to those observed before the patient started pantoprazole therapy. During this period, her serum magnesium level was inversely related to her systolic and diastolic blood pressure (Pearson correlation coefficients, $-0.82$ and $-0.83$, respectively; $P < 0.05$).

After the patient gave consent, we readministered pantoprazole, 40 mg/d, with calcium and magnesium supplementation. She had an elevated blood pressure (140/90 mm Hg) and decreased serum magnesium concentration (0.53 mmol/L [1.06 mEq/L]) 4 days later. We advised her not to take PPIs in the future. During 2 years of follow-up, the patient has had no exacerbations of Crohn disease, some requiring surgery, but no tetany, arterial hypertension, or major electrolyte abnormalities.

Discussion: The patient had no history of arterial hypertension, and we ruled out renal or endocrine causes of arterial hypertension. Other investigators have reported that magnesium affects vascular tone by several mechanisms, one of which is competing with calcium and modulating the level of intracellular total and free calcium (4, 5). We suggest that magnesium and calcium be measured during PPI administration, particularly in patients with malabsorption or prehypertension.

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References

Spuriously High B-Type Natriuretic Peptide Level Caused by Human Antimouse Antibodies

Background: Assays for B-type natriuretic peptide (BNP) are widely used in clinical practice to help confirm or refute the diagnosis of heart failure in patients with dyspnea (1).

Objective: To describe how we determined the cause of a falsely high BNP level.

Case Report: Clinicians asked us to consult on a 61-year-old man admitted to our hospital with suspected diastolic heart failure and persistently elevated serum BNP levels. The patient had previously been treated for dyspnea and chest discomfort and had a history of hypertension. Our laboratory measured a serum BNP level of 3234 ng/L (normal range, 0 to 80 ng/L; Abbott AxSYM assay, Abbott Diagnostics, Abbott Park, Illinois). Prior serum BNP levels were greater than 4000 ng/L and 3798 ng/L at 6 months and 3 months before admission, respectively. Hepatic and renal function, lipid levels, and chest radiography were normal. Echocardiography showed normal ejection fraction with a lower peak velocity for mitral A-wave than for mitral A-wave. Cardiac catheterization showed normal pressures in the right atrium, right ventricle, pulmonary artery, and pulmonary capillary wedge. Angiography showed no stenosis in the coronary arteries. The results of other diagnostic tests, including serum levels of rheumatoid factor, immunoglobulin, complement, and troponin-I level, and thyroid function, were within normal limits.

Because we could not establish clinical heart failure as a cause for the high BNP levels, we consulted clinical laboratory experts, who advised us that an interfering antibody could explain our findings. The patient denied any therapy with biological products, including inoculation. He recalled that 38 years earlier, a mouse bit his finger badly enough to cause bleeding, but the wound healed without medical intervention.

Our hospital laboratory measured serum BNP simultaneously by using its usual assay and an alternative assay (Triage BNP, Biosite, San Diego, California); elevated values were found with the usual assay (1890.3 ng/L), but normal values were found with the alternative assay (6.40 ng/L; normal range, 0 to 80 ng/L). The laboratory found normal values for N-terminal fragment of prohormone BNP (60 ng/L; normal range, 0 to 161 ng/L; Roche Cardiac Cobas assay, Roche Diagnostics, Mannheim, Germany). We concluded that the BNP levels measured with our usual assay were falsely high, although we could not be confident of the cause. The patient was discharged.

Our laboratory later added heterophilic blocking reagent 1 (Scantibodies Laboratory, Santee, California) to the patient’s serum and found reduced BNP levels of 1170.54 ng/L with the usual assay. The laboratory also found human antimouse antibody in his serum at a level of 40.5 ng/L, which exceeded the upper limit of normal (12.5 ng/L). In addition, we retested the patient 2 years later with the hospital’s usual BNP assay and found levels greater than 4000 pg/mL.

Discussion: Falsely high BNP results usually are caused by factors that interfere with the BNP assay (2, 3). Most BNP assays are 2-site assays, which are also known as “sandwich assays.” They involve 2 nonhuman, animal antibodies that are directed against different parts of the target molecule. One antibody captures the target and binds it to a solid surface. When the other antibody binds to the target, it produces a signal (often chemoluminescent) with an intensity that reflects the target level—in this case, BNP. A human antibody directed against the animal antibodies in assays can bind to both antibodies and produce a signal that cannot be distinguished from the target signal. The assays we used to test for BNP use mouse antibodies. The capture antibodies in both assays are directed against the same BNP epitope, but the signal antibody in our usual assay is a monoclonal antibody directed against the carboxy-terminal end of BNP, whereas the signal antibody in the alternative assay is a polyclonal antibody directed against the amino-terminal end of BNP. These differences may explain why higher values were reported with our usual assay and normal values with the alternative assay.

The assay used to measure N-terminal fragment of prohormone BNP uses sheep antibodies, which would not be affected by anti-
mouse antibodies in our patient’s serum. Heterophilic blocking reagent 1 contains mouse immunoglobulins that prevent human anti-mouse antibodies from binding to mouse antibodies, and probably explains why addition of this reagent to the patient’s serum reduced BNP levels with our usual assay. As the antibodies in BNP assays are often derived from mice, a human antimouse antibody more commonly interferes with BNP assays than human antibodies directed against other animals (4, 5).

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References

CORRECTIONS

Correction: A New Equation to Estimate Glomerular Filtration Rate

The following errors have recently been discovered. None of the errors substantially affects the results or conclusions of the study (1).

In Table 4, there is a typographical error in the number of patients with concordant estimated glomerular filtration rate (eGFR) of 30 to 59 mL/min per 1.73 m² (using CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] and MDRD [Modification of Diet in Renal Disease] study equations) with measured GFR >90 mL/min per 1.73 m². The number of patients should be 18 (0.5%) rather than 118 (3.0%).

In Appendix Table 4, 125 patients enrolled in the Nephrotest study were included twice, so the total number of patients study should be 313 rather than 438. Consequently, in Table 1, the number of patients included in the validation data set should be 3771 rather than 3896. This error does not affect the validation of the new equation.

In Appendix Table 9, the prevalence of CKD stages 1 through 4 in women, computed using the CKD-EPI equation was erroneously copied from the prevalence computed using the MDRD study equation. The number in 1000s (95% CI) should be as follows: 13 582 (12 410 to 14 771) for stages 1 through 4; 2583 (1955 to 3241) for stage 1; 2595 (2011 to 3209) for stage 2; 7948 (7171 to 8731) for stage 3; and 456 (297 to 614) for stage 4.

Reference

Correction: Smoking, Smoking Cessation, and Risk for Symptomatic Peripheral Artery Disease in Women

The title for the recent article by Conen and colleagues (1) should have said “Smoking Cessation” as opposed to “Smoking Status.”

This has been corrected in the online version.

Reference

Correction: Screening for Bladder Cancer: U.S. Preventive Services Task Force Recommendation Statement

In the last paragraph of a recent recommendation statement (1), the phrase, “however, it is currently reviewing this recommendation” should have been deleted. The statement should read, “In 2011, the American Academy of Family Physicians endorsed the USPSTF recommendation.”

This has been corrected in the online version.

Reference