

Health Outcomes Among Patients Treated by Nurse Practitioners or Physicians

To the Editor: The study by Dr Mundinger and colleagues¹ compared the health outcomes of patients treated by nurse practitioners to those treated by physicians in primary care settings that were similar in terms of responsibilities and patient panels. There was no description of the training of either the physicians or the nurses in the study, other than that they were all faculty members. The authors state, "The combination of authority to prescribe drugs, direct reimbursement from most payers, and hospital admitting privileges creates a situation in which nurse practitioners and primary care physicians can have equivalent responsibilities." This combination does not include core elements of medical care such as evaluation, diagnosis, and treatment of undifferentiated patients. Patients with previously diagnosed and treated asthma, diabetes, and hypertension could be cared for successfully in a limited time frame by a person with less training than a physician. Each of these conditions has very clear treatment guidelines.

The most troublesome aspect of the study is the outcome measure. Although the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is a well-established measure of health status, it assesses only self-reported perception of health. Furthermore, the sensitivity of the SF-36 for detecting longitudinal change within patients has been questioned.² Patient satisfaction may be important but in itself is not a measure of the ability to provide many of the complicated aspects of patient diagnosis and care.

In the accompanying Editorial,³ Dr Sox states that the study has strong internal but weak external validity, and thus the conclusions of this study cannot be generalized. They are highly limited to this particular patient population and clinical structure and the relatively brief period of this study.

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1. Mundinger MO, Kane RL, Lenz ER, et al. Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial. *JAMA*. 2000;283:59-68.

2. Edelman D, Williams GR, Rothman M, Samsa GP. A comparison of three health status measures in primary care outpatients. *J Gen Intern Med*. 1999;14:759-762.

3. Sox HC. Independent primary care practice by nurse practitioners. *JAMA*. 2000;283:106-107.

To the Editor: The article by Dr Mundinger and colleagues¹ concluded that nurse practitioners with the "same authority, responsibilities, productivity and administrative requirements, and patient population" had "comparable outcomes to primary care physicians." However, its implication that primary care given independently by nurse practitioners is equivalent to that provided by physicians cannot be concluded from this study.

First, patients were followed up for only 6 months, too brief an interval to accurately assess the quality of care. In primary

care, the typical patient-physician relationship spans a much longer period. This ongoing relationship, which is the hallmark of primary care, demands considerable skill as patients' medical conditions evolve, progress, and, ideally, stabilize and improve. The continuity of primary care is in stark contrast with the 0 to 2 ambulatory visits noted in 60% of the study sample.

Second, the mean age of the patients in this sample was 45.9 years, with 76.8% women and 90.3% of Hispanic background. This sample certainly is not representative of most primary care practice. As mentioned in the accompanying Editorial,² health outcomes in this young, predominantly Hispanic population are usually good.

Finally, no information was given about the physicians' or nurse practitioners' level of experience. This information is extremely pertinent; cumulative clinical experiences reinforce and hone physicians' knowledge base, thereby significantly improving their effectiveness, efficiency, and competency. In my own experiences as a second-year resident in internal medicine, I am definitely more competent in the ambulatory setting than I was as an intern. There is an ongoing learning curve for physicians in the primary care setting.

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1. Mundinger MO, Kane RL, Lenz ER, et al. Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial. *JAMA*. 2000;283:59-68.

2. Sox HC. Independent primary care practice by nurse practitioners. *JAMA*. 2000;283:106-108.

To the Editor: Dr Mundinger and colleagues¹ provide an excellent comparison of the care provided by nurse practitioners and primary care physicians from several perspectives.

In considering their work, though, one must also note certain limitations. Hypertension, asthma, and diabetes, while chronic conditions, do not generally warrant frequent admission to the hospital. Therefore, differences in the rate of emergency department use, hospitalization, and mortality may not be evident for some time beyond the 1-year length of the study.

Another important limitation is the assessment of the quality of care provided by both groups as reflected by physiologi-

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Letters Section Editors: Phil B. Fontanarosa, MD, Deputy Editor; Stephen J. Lurie, MD, PhD, Contributing Editor.

cal parameters. No differences were noted in peak flows or glycosylated hemoglobin (HbA_{1c}) measurements. Peak flow rates, however, were not controlled for age, height, or deviation from the norm. Furthermore, the average HbA_{1c} levels were surprisingly high—9.4% for the physician group and 9.5% among patients of nurse practitioners.

This poor level of control is remarkable. In our community health center in rural Colorado, we serve a poor, primarily Hispanic population, similar to the sample in this study. Currently, we are staffed only with physicians. Chart review for the last 5 months shows an average HbA_{1c} level of 6.9% for the most recent tests performed in our patients. Overall, it is 7.4% for all tests performed.

It is well established that HbA_{1c} should be maintained as low as possible (ideally, $\leq 7.0\%$) to decrease long-term complications of diabetes. In the study by Mundinger et al, neither nurse practitioners nor physicians brought their patients to a level of glycemic control that is recommended by the American Diabetes Association.² In assessing quality of care, the highest standard of comparison must be used.

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1. Mundinger MO, Kane RL, Lenz ER, et al. Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial. *JAMA*. 2000;283:59-68.

2. American Diabetes Association. Clinical practice recommendations 2000. *Diabetes Care*. 2000;23(suppl 1):S1-S116.

To the Editor: Dr Mundinger and colleagues¹ state that their results support the “hypothesis” that there is no difference in patient outcomes between nurse practitioner and physician care. However, this is really the null hypothesis, and their study simply failed to find a difference. This seemingly semantic argument actually has an important basis—that of the difference between statistical and clinical significance. Current research methods may provide only a blunt tool with regard to dissecting what must predictably be small but nonetheless important shades of gray in primary care outcomes.

It is not surprising that among a group of 1316 patients—a fraction of a typical family physician’s yearly caseload—most would experience a benign course during the study’s 6- to 12-month follow-up period. It would be more interesting to focus on the exceptional cases—the few sick individuals who may have subtle signs of disease. The authors fail to discuss the interesting trends of “sicker patients” evident in Table 5 of their article, except to dismiss the results as nonsignificant. However, the results do imply a trend toward greater use of specialists, emergency departments, urgent care centers, and hospitals among the group cared for by nurse practitioners. That these trends fail to reach statistical significance suggests the possibility of insufficient power in this study, not that the null hypothesis was proved.

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1. Mundinger MO, Kane RL, Lenz ER, et al. Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial. *JAMA*. 2000;283:59-68.

To the Editor: The study by Dr Mundinger and colleagues¹ describes outcomes of patients treated by nurse practitioners or physicians. Although outcomes of these groups were similar at the end of the study, it is not clear that this result was solely due to the quality of care provided. Although the authors state that “. . . a similar number of patients were scheduled per session in each clinic,” it is likely that with the introduction of the new nurse practitioner clinic, fewer patients were seen at the new site per clinic session during the early part of the study. This is important because it is generally recognized that patient satisfaction is closely related to the length of time that a practitioner spends with a patient. It has also been demonstrated that patient satisfaction correlates strongly with patient adherence.² Measuring the differences in productivity between the 2 groups would give a clearer picture of the total caseload of each group of practitioners during the study.

Another notable finding in the study is the rather poor control of both diabetes and asthma found at the conclusion of the study. These findings are consistent with many studies demonstrating suboptimal control of these conditions in many primary care populations, regardless of clinician training.³ It is unfortunate and somewhat puzzling that these measurements were recorded only at the conclusion of the study. Because of this, the true impact of treatment received during the study cannot be accurately assessed. Particularly in this socioeconomically disadvantaged and transient population, issues of nonadherence and other urgent competing health and psychosocial demands could have easily overshadowed any differences in quality of care provided during the short follow-up period, and the outcomes may have been similar regardless of the quality of care available.

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1. Mundinger MO, Kane RL, Lenz ER, et al. Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial. *JAMA*. 2000;283:59-68.

2. Safran DG, Taira DA, Rogers WH, Kosinski M, Ware JE, Tarlov AR. Linking primary care performance to outcomes of care. *J Fam Pract*. 1998;47:213-220.

3. Ornstein SM, Jenkins RG. Quality of care for chronic illness in primary care: opportunity for improvement in process and outcome measures. *Am J Manag Care*. 1999;5:621-627.

To the Editor: Several methodological flaws limit the conclusions of Dr Mundinger and colleagues.¹ First, patients were randomized but not analyzed according to an intention-to-treat analysis. Seventy-nine percent of patients enrolled in the study completed the 6-month follow-up interview but only 66% of patients randomized in the study were actually enrolled. Thus, only 52% of randomized patients completed the study through the 6-month follow-up interview. Physiological and follow-up data on satisfaction and self-reported health status were derived from this 6-month follow-up interview. Drawing conclusions from such a low proportion of randomized patients

may introduce confounding, which might have been avoided by assessing health status at the time of randomization.

Second, the authors found no differences in 3 of 4 physiological measures after 6 months. However, a baseline set of measures would have allowed the authors to correct for baseline variation between the 2 groups, since randomization does not ensure equality of baseline measures.²

The autonomy of nurse practitioners has become a contentious issue in today's medical marketplace. Further data, including severity-adjusted process of care and outcome measurements, analysis of random groups by intention-to-treat analysis, and longer lengths of follow-up, will be needed to establish a consensus on the optimal integration of nurse practitioners.

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1. Munding MO, Kane RL, Lenz ER, et al. Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial. *JAMA*. 2000;283:59-68.

2. Friedman LM, Furberg CD, DeMets DL. *Fundamentals of Clinical Trials*. 3rd ed. New York, NY: Springer-Verlag NY Inc; 1998.

To the Editor: In his Editorial regarding the study by Dr Munding and colleagues,¹ Dr Sox² correctly observes that even though nurse practitioners competently treated mostly young patients requiring routine care for hypertension and diabetes, they might not obtain such favorable outcomes when treating acute complications or older, sicker patients. However, it does not follow, as Sox implies, that nurse practitioners should therefore be barred from practicing independently. Nor should we, as physicians, monopolize routine care simply because we can handle more complex medical problems.

Despite widespread dissatisfaction with managed care, payers (eg, insurers, government, employers) clearly have indicated that they will resist further increases in the cost of health care. They will not pay physician-level fees for care that can be competently provided by less-skilled professionals. If we continue to do nurse practitioner-level work, we must be satisfied with nurse practitioner-level reimbursement. The only way for physicians to maintain their incomes is to see more patients in the same amount of time, which, in turn, makes it more difficult to care for complicated patients only we can treat.

Our dilemma as physicians is not dissimilar to the problems currently facing US textile workers, who are watching their jobs migrate to equally competent workers in low-wage countries. They must either accept the lower wage, set up trade barriers, or upgrade their skills.

Since we cannot compete with nurse practitioners on price, we will have to adopt other strategies. We should work in teams. Every health professional should know his or her limits and exceed them at his or her own peril. Primary care physicians need to move from high-volume, low-margin services to low-volume, high-margin services. This is a benefit of integrating care.

As Sox correctly observes, ceding some work to nurse practitioners may reduce the demand for physicians. However, the public—as patients and as taxpayers—is under no obligation to support whatever number of physicians is produced. We can reduce the supply of physicians without triggering antitrust laws simply by decreasing admission to medical schools and residencies. Indeed, if medical education is as expensive a drain on the system as is commonly claimed, this strategy should save everyone money.

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1. Munding MO, Kane RL, Lenz ER, et al. Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial. *JAMA*. 2000;283:59-68.

2. Sox HC. Independent primary care practice by nurse practitioners. *JAMA*. 2000;283:106-107.

To the Editor: As nurse practitioner faculty leaders, the Board of Directors of the National Organization of Nurse Practitioner Faculties commends the important research reported by Dr Munding and colleagues.¹ Our organization has worked hard to establish standards of quality in nurse practitioner education and is in the vanguard of organizations seeking to promote quality in primary care. We agree with Dr Sox² that this is an excellent and well-executed study. However, we wish to reply to other comments in his Editorial.

First, Sox claims that the brief period during which study data were collected detracts from the study's external validity. Although the findings should not be generalized to long-term management of chronically ill individuals, the data clearly indicate that nurse practitioners and physicians provided care that resulted in similar outcomes. Previous studies have primarily involved healthy populations, making this study of particular interest. Sox neglects to mention that 1-year data regarding primary and specialty care visits, emergency and urgent care visits, and hospitalizations did not differ significantly between patients cared for by nurse practitioners and physicians, further supporting the similarities in outcomes.

Second, although better pregnancy outcomes have been documented for Hispanic women, diabetes occurs in this population at a higher rate than in whites, and inner-city groups are known to have a higher prevalence of asthma resulting from inadequate housing and environmental agents. The 30% prevalence rate of hypertension in a relatively young group of women indicates that this group was not healthier than the general population.

Third, nurse practitioners have always consulted physicians and other nurse practitioners when caring for patients who do not respond to treatment. The goal of nurse practitioner practice is not to replace or supplant physicians but, rather, to increase access to quality health care for the many patients whose health care needs fall within the nurse practitioner's scope of practice. In this role, nurse practitioners provide important services and free physicians' time to focus on the high-level diagnostic and therapeutic services for which they have been trained. Consultation and collaboration are essen-

tial skills for nurse practitioners, as they are for all members of the health care team.

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1. Mundinger MO, Kane RL, Lenz ER, et al. Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial. *JAMA*. 2000;283:59-68.
2. Sox HC. Independent primary care practice by nurse practitioners. *JAMA*. 2000; 283:106-107.

In Reply: Many of the above comments challenge the generalizability of our findings. We appreciate this limitation but believe that our results are suggestive enough to open more active discussion about the appropriate role of various primary care practitioners.

Dr Bagley, Dr Chan-Tack, Dr Hicks, and Dr Rayburn all raise questions about the supposed healthy nature of our population and the relative ease of using practice guidelines to care for patients with chronic conditions. The high burden of illness in the population is reflected in their SF-36 scores, which were 35% lower on average than a national sample of similar age and sex.¹ Moreover, very few patients had only a single previously diagnosed condition. Less than 5% (58 of 1316) of the study patients were treated in the first 6 months of the study for only 1 of the chronic conditions (or for a related diagnosis) or had a general medical examination.

Hicks and Dr Nasir question the poor diabetic control both types of practitioners achieved. The good results achieved with a Hispanic population in Colorado are commendable. We do not know how ours population differs from that in Colorado, but we do know ours was poor, minority, exceptionally transient, and had a high burden of illness. The number of patients scheduled and seen was similar in both physician and nurse practitioner clinic sites; the higher enrollment in the nurse practitioner cohort attests to the greater number of appointments available in the newer nurse practitioner clinic.

Bagley questions the validity of the SF-36 in detecting differences over time in patients. This instrument has been used in many other studies to detect such change.²⁻⁴ The SF-36 was certainly sensitive enough to track improvement in the study patients' conditions from the time of their initial emergency department visit through the several follow-up points. Moreover, we also used physiological measures and utilization data to complete our analysis.

We agree that the brief time frame for the study was a problem. It represented a trade-off between sample loss and time to observe an effect. All practitioners in the study were salaried, part-time employees of hospital-based primary care clinics, and all were full-time faculty in either the medical or nursing school. No house staff were involved.

Rayburn raises questions of statistical power. Studies designed to show equivalency rather than differences require careful attention to this issue, which we addressed at some length. In planning the study we anticipated the issue of statistical power in calculating our sample size because the primary hypothesis was for no difference between physician and nurse practitioner practices. We confirmed our original calculations with the actual data

and concluded that the findings would not have changed with a larger sample. Indeed, it would require a very large sample to produce statistically significant differences, and these differences would not consistently favor the physician group.

Intention-to-treat analysis was not used because it would exacerbate the problems of a study designed to assess comparability; it fosters a conservative test of differences. Baseline physiological measurements would have been very helpful, but the logistics of randomization prevented us from obtaining them.

No single study will satisfactorily resolve a controversial issue. We hope this study will encourage similar efforts to test new primary care models.

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1. Ware JE, Kosinski M, Keller SD. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Boston, Mass: Health Institute, New England Medical Center; 1994.
2. Ware JE, Bayliss MS, Rogers WH, Kosinski M, Tarlov AR. Differences in 4-year health outcomes for elderly and poor, chronically ill patients treated in HMO and fee-for-service systems: results from the Medical Outcomes Study. *JAMA*. 1996;276:1039-1047.
3. Garratt AM, Ruta DA, Abdalla MI, Russell IT. SF-36 health survey questionnaire, II: responsiveness to changes in health status in four common clinical conditions. *Qual Health Care*. 1994;3:186-192.
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In Reply: I agree with most of Dr Poplin's comments. I disagree with her contention that we should encourage nurse practitioners to practice independently, without requiring them to prove that they measure up to physicians in caring for very sick patients. Our society requires the proponents of new drugs and new tests to prove that the new technology is as effective as the established technology. In this way, those who pay for health care, or those who use it, can decide whether the new technology is effective in a specific situation. Shouldn't patients know if physicians are better than nurse practitioners at some aspect of primary care so that they can decide when to ask for a consultation?

The letter from the Board of Directors of the National Organization of Nurse Practitioner Faculties takes issue with several examples that I used to support my critique of the study by Dr Mundinger and colleagues.¹ I contend that utilization of health care after 1 year is a measure of the quantity of health care, not the quality of its outcomes. Although Hispanic populations may have a higher prevalence of some diseases, they have lower mortality rates than their socioeconomic status would predict. The Board of Directors of the National Organization of Nurse Practitioner Faculties contends that nurse practitioners have always consulted physicians. I regret that the study by Mundinger et al does not offer an account of collaboration and consultation.

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1. Mundinger MO, Kane RL, Lenz ER, et al. Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial. *JAMA*. 2000;283:59-68.

Human Papillomavirus Testing as a Screening Tool for Cervical Cancer

To the Editor: In their study of the utility of testing for high-risk human papillomavirus (HPV) in underprivileged women in rural Costa Rica, Dr Schiffman and colleagues¹ suggested that in women older than 35 years, this test is comparable or even superior to the Papanicolaou (Pap) test. The concept of HPV infection as an important factor in the genesis of cancer of the uterine cervix is based on the observation that the DNA of "high risk" viruses is commonly found in nearly all invasive cancers and that viral proteins may impede events in the normal cell cycle.² The initial theory that the mere presence of high-risk HPV is tantamount to a precancerous or malignant lesion of the uterine cervix is no longer tenable today because of very high rates of transient infections observed in sexually active young women.³ Thus, HPV testing in women aged 18 to 35 years, the age at which most of the important precancerous events occur, would be highly misleading and could result in an inordinately high level of referrals for colposcopy, perhaps as high as 30%. In the study by Schiffman et al, the rate of referral for colposcopy for women aged 18 to 30 years based on HPV testing was 21%, and 11% of women in all age groups had false-positive HPV test results.

Because of the high frequency of HPV infection in younger women, it is now thought that older women with persisting infection with a high-risk virus are at greatest risk for cervical cancer. However, even in this group of women, only a small percentage develop high-grade precancerous lesions.⁴ Waiting until the age of 35 or 40 years to test for the presence of high-risk HPV infection with some measure of reliability would put the lives of many younger women in serious jeopardy. Schiffman et al found 12 invasive cervical cancers, clearly showing that these women should have been tested many years earlier. Furthermore, to test for persistence of the virus would require 2 or more sequential tests which, in 1 study cited,⁴ were triggered by high-grade cytologic abnormalities identified in Pap test results. It has been shown that Pap tests not only have a significant false-negative rate⁵ but that the precise cytologic classification of low-grade vs high-grade lesions is often inaccurate.⁶

There is little doubt that additional research on the significance of HPV in cervical cancer is warranted, but, in my judgment, there is no evidence that the technique of testing for HPV is currently mature enough to replace the Pap test as a screening test, particularly in younger women who should be the primary target of these efforts. To be sure, the accuracy of the Pap test is far from perfect,^{5,6} and improvements in its performance would be welcome, but this may require better quality control, additional time needed to screen the material adequately, and better training of cytotechnologists and cytopathologists in the interpretation of this complex test.

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1. Schiffman M, Herrero R, Hildesheim A, et al. HPV DNA testing in cervical cancer screening: results from women in a high-risk province of Costa Rica. *JAMA*. 2000;283:87-93.
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6. Koss LG. Cervical (Pap) smear: new directions. *Cancer*. 1993;71(suppl 4):1406-1412.

In Reply: We agree that HPV DNA testing should not be used alone for general screening of young women because of the high prevalence of infection in this age group. However, the complementary strengths of HPV testing and Pap screening can improve cervical cancer prevention.

Oncogenic types of HPV cause nearly all cases of cervical carcinoma.¹ In fact, viral DNA persistence is necessary for the development of high-grade precursors and carcinomas.^{2,3} Consequently, HPV DNA testing is the most sensitive screening tool for the detection of serious cervical neoplasia.⁴ This high sensitivity is critical, because, as a corollary, the predictive value of a negative HPV test result is extremely high. The superior negative predictive value of HPV DNA testing may safely permit longer screening intervals, in addition to aiding in the triage of women with equivocal Pap test results.

Cytologic screening for carcinoma, immediate high-grade precursors, and HPV infection remain more specific than DNA testing. The grading of cytologic abnormalities is particularly informative, especially for the severe grades that indicate high risks of serious neoplasia (positive predictive value). Unlike Dr Koss, we believe that it will prove difficult to improve the moderate rate of interpathologist agreement on grading much further, given the difficult distinctions.

Koss is particularly concerned about false-positive HPV test results. False-positive HPV DNA results obtained from the highly reproducible commercial kit usually represent true infections without serious neoplasia in young, sexually active women. We must develop clear public health messages that distinguish between single-time detection of any HPV and persistent infections with an oncogenic type. It is persistent infections that convey a greatly elevated risk of future high-grade neoplasia.^{2,3} The addition of HPV DNA testing to cervical cytologic screening will be most effective in older women past the peak incidence of acute infections, or in programs of repeat testing that assess viral persistence.

Pap testing has an acknowledged record of reducing cervical cancer mortality when systematically applied in a program of repeated screening. Unlike Koss, we believe that the accumulated evidence already supports introduction of HPV DNA testing to supplement cervical cytology in selected situations.⁴ At the minimum, DNA testing can already be recom-

mended to standardize cytologic diagnoses in different laboratories.⁵

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2. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med.* 1998;338:423-428.
3. Nobbenhuis MA, Walboomers JM, Helmerhorst TJ, et al. Relation of human papillomavirus status to cervical lesions and consequences for cervical-cancer screening: a prospective study. *Lancet.* 1999;354:20-25.
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Elevated Liver Enzymes Following Initiation of Antiretroviral Therapy

To the Editor: Dr Sulkowski and colleagues¹ described hepatotoxicity associated with antiretroviral treatment (ART), but the finding of liver abnormalities following ART does not necessarily imply drug toxicity. Recent reports have suggested that protease inhibitor therapy may be associated with transient “flares” of chronic viral hepatitis, which represent a reactivation of the host inflammatory response following the “immune reconstitution” associated with successful ART. Similar inflammatory reactivations of clinically silent infections have been described for other opportunistic infections after human immunodeficiency virus (HIV) ART.² Indeed, anecdotal reports have shown that the flare of hepatitis may be followed by full clearance of the hepatitis B virus.^{3,4}

Mild to severe hepatotoxicity may be the initial sign of immune reconstitution. If ART is discontinued at this point, such cases may be indistinguishable from those of drug toxicity. Sulkowski et al reported that in 6 of 31 cases with severe hepatotoxicity, ART was continued without clinically significant consequences. Unfortunately, no information regarding the evolution of viral hepatitis markers was provided. Interestingly, an increase in CD4 cell count was found to correlate with severe hepatotoxicity. The authors interpreted this result as a possible marker of better adherence to therapy. However, the correlation of the increase of CD4 cell count and liver function abnormalities would also be expected if these phenomena were related to an increased host response to hepatitis virus after an improvement in the immunological status. Indeed, cell-mediated immunity is considered to play an important role in the clearance of viral hepatitis infection.

Although this was not the original purpose of the study, it would be of great interest to know the ultimate evolution of viral markers of these patients, and whether there was clearance of the hepatitis B or C virus in any of them. If this were the case, the appearance of liver function abnormalities after ART might represent an immune reconstitution syndrome rather than an adverse outcome.

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1. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with ART therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA.* 2000;283:74-80.
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In Reply: We agree with Drs Velasco and Guijarro that serum aminotransaminase level elevations following the initiation of ART could reflect immune reconstitution, as we discussed. However, there are a number of reasons to suspect that the majority of significant liver enzyme elevations in our study were due to medication toxicity. Liver enzyme elevations occurred more often in persons receiving a specific drug, ritonavir, an effect that was independent of effectiveness of the medication in suppressing HIV replication. In addition, 14% of persons with ritonavir-associated hepatotoxicity did not have effective suppression of HIV replication or increases in CD4 cell count, findings that essentially exclude immune reconstitution in these cases.

Velasco and Guijarro suggest that serial assessment of hepatitis C virus (HCV) RNA level may reveal decreases in HCV viremia and offer evidence of immune reconstitution syndrome. For instance, reduction in cytomegalovirus viremia has recently been demonstrated following highly active antiretroviral therapy (HAART)-associated immune restoration.¹ However, studies that have examined HCV RNA levels after HAART have failed to find evidence of HCV-specific immune reconstitution. Rutschmann et al² and Ragni and Bontempo³ found that HCV RNA levels increased after initiation of HAART despite increases in CD4 cell count, and Ragni and Bontempo³ reported that HCV RNA levels decreased with the discontinuation of HAART.

In addition, immune reconstitution typically refers to the restoration of antigen-specific effects, and paradoxical worsening of disease activity has been demonstrated for some pathogens, such as *Mycobacterium tuberculosis*.⁴ However, given the current understanding of HCV persistence, one might be surprised to find many individuals who would develop clinically detectable disease with restoration of an immune response that was previously ineffective in containing persistent HCV variants. Furthermore, in our study the proportion of patients who

developed hepatotoxicity in association with CD4 cell count elevations was not different in HCV-infected (94%) vs HCV-uninfected (83%) individuals. In fact, 42% of all hepatotoxicity was observed in HCV-uninfected individuals.

Antiretroviral therapy-associated hepatotoxicity is probably multifactorial and different mechanisms could dominate in various hosts. For example, immune reconstitution to another pathogen (eg, hepatitis B virus) could indirectly affect levels of HCV RNA, and may have been responsible for some of the cases in our study. We are not aware of any study, including our own, that was designed to evaluate the mechanism of ART-associated hepatotoxicity. Until such data are available, investigators will need to keep an open mind about the subject.

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Prognostic Criteria for Hospice Eligibility

To the Editor: Dr Fox and colleagues¹ make a significant contribution to the palliative care-hospice field by demonstrating the limitations of predicting the time of death in patients with terminal diseases. The findings lend further support to the call of the National Hospice Organization (NHO) for the elimination of local medical review policies (LMRPs) to justify hospice referrals for Medicare beneficiaries.

These policies not only expand the authority of the intermediary beyond the scope of the law that created hospice under Medicare, but they also diminish the role of physician judgment in the referral process. As this study demonstrates so well, the guidelines require further development for them to achieve prognostic confidence and accuracy. Indeed, they were intended only as a first step on the road to prognostic sophistication.

Unfortunately, Medicare intermediaries latched onto the guidelines in an effort to produce a standardized basis for referrals to hospice. In effect, they converted the guidelines from sufficient conditions for having the conversation about end-of-life care to necessary causes, in the form of LMRPs. The result is that hospices must now demonstrate and document that patients with congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), end-stage liver disease (ESLD), and other diseases meet the conditions specified in the LMRPs. This has the effect of further reducing

the availability of hospice care to the very people who would most benefit from it.

In April 1999, the NHO recommended eliminating the use of NHO guidelines for noncancer diseases as a basis for LMRPs. The guidelines were intended not only to stimulate evaluation of patients for hospice care, but also to promote discussion about advance planning for end-of-life care. At best, they were designed as sufficient criteria for referral evaluation.

Despite our wishes and efforts to enhance prognostic accuracy, the best prognostic tool is physician judgment. In the original hospice legislation, Congress recognized in law that the art of prognosticating should be in the physician's hands.² Until reliability can be established through tested guidelines, it should remain there.

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2. 55 *Federal Register* 50834 (1990).

In Reply: We agree with Mr Simpson that prognostic guidelines cannot accurately identify patients who will die within 6 months. We disagree, however, with his suggestion that "the guidelines require further development for them to achieve prognostic confidence and accuracy." To the contrary, as we stated in our article, "the goal of determining in advance—with a high degree of accuracy—which individual patients with COPD, CHF, or ESLD will die within 6 months is unrealistic." These patients typically die as a result of sudden, unpredictable events. Thus, policy should not assume that precision in prognosis is possible. Instead, eligibility for comprehensive end-of-life care should be based on severity of illness, and modified by patient preferences and service needs.

As we acknowledged in our article, it may be possible to predict 6-month survival somewhat more accurately using factors other than those we analyzed. However, even though hospice programs may be able to identify a small population with reliably dire short-term prognoses, our community must still meet the needs of the much larger population of patients who are very sick and dying of advanced chronic disease. Most such patients are not eligible for hospice care under current guidelines because their life span cannot be predicted with precision. We agree that health care policymakers should ensure comprehensive end-of-life services to all dying patients.

Disclaimer: The views expressed in this letter do not necessarily represent the views of the Department of Veterans Affairs.

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