7. Sedlacek M, Gemery JM, Cheung AL, Bayer AS, Remillard BD. Aspirin treatment is associated with a significantl decreased risk of *Staphylococcus aureus* bacteremia in hemodialysis patients with tunneled catheters. Am J Kidney Dis **2007**; 49:401–8.

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## Determination of the Incidence of Tuberculosis in Low-Income Countries

To the Editor—We read with interest the report by The Antiretroviral Therapy in Low-Income Countries Collaboration of the International epidemiological Databases to Evaluate AIDS (IeDEA) and The ART Cohort Collaboration on tuberculosis (TB) after initiation of antiretroviral therapy in low-income and high-income countries [1]. The authors do not mention the number of patients who were already receiving treatment for TB when the antiretroviral therapy was started (were the data not available?). However, they do mention that programs in lower-income countries routinely screened patients for TB before they commenced HAART. It is unclear to us whether patients being given treatment for TB at the start of HAART were included in the analysis. We propose that they should have been excluded from the study population if the aim of the study was to determine the incidence of TB and to compare the incidence rate-ratios for new TB infections. Indeed, in contrast to in high-income countries, in low-income countries, TB is one of the main reasons to initiate HAART. In Malawi, for example, from July through September 2005, 12% of the patients who started HAART did so because of TB [2]. During treatment for TB, by definition these patients cannot develop a new TB infection. We suppose that, if this approach were taken, the conclusions of the report would remain the same, but the calculations may change slightly. If the number of patients not receiving treatment for TB who started HAART is used as the denominator, the real incidence of TB in low-income countries will be even higher, particularly soon after the initiation of HAART.

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### References

1. The Antiretroviral Therapy in Low-Income Countries Collaboration of the International epidemiological Databases to Evaluate AIDS (IeDEA) and The ART Cohort Collaboration. Tuberculosis after initiation of antiretroviral therapy in low-income and high-income countries. Clin Infect Dis **2007**; 45:1518–21.
2. Makombe SD, Harries AD, Yu JK, et al. Outcomes of tuberculosis patients who start antiretroviral therapy under routine programme conditions in Malawi. Int J Tuberc Lung Dis **2007**; 11:412–6.

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## Reply to Colebunders and Caluwaerts

To the Editor—We thank Colebunders and Caluwaerts [1] for their interest in the recent analysis by The Antiretroviral Therapy in Low-Income Countries Collaboration of the International epidemiological Databases to Evaluate AIDS (IeDEA) and The ART Cohort Collaboration [2]. In this collaborative study, we compared the incidence rates of tuberculosis (TB) among patients receiving HAART in low-income and high-income countries. Colebunders and Caluwaerts ask whether the analysis included patients who were receiving treatment for TB at the start of HAART and argue that, if so, this might have biased the incidence rates of TB downward in lower-income countries and might have distorted the incidence-rate ratios during the firs year of HAART.

As Caluwaerts and Colebunders [1] suspected, data on treatment for TB at the time of initiation of HAART were not available for all the cohorts from low-income countries. But note that, as we pointed out in our report [2], the main objective of the analysis was not to estimate absolute rates but was to compare relative changes in rates of TB during the firs year of HAART in low-income and high-income settings. The incidence rates obtained in such an analysis of data from 15 different sites were a weighted average of site-specifi rates, influence by variation in background rates and diagnostic procedures, and are not applicable to any specifi setting.

We repeated analyses for 9 low-income cohorts with data on previous treatment for TB, including 2050 patients who were not receiving treatment when HAART was started. Among these patients, the incidence of TB in the firs year of HAART was 8.8 cases per 100 person-years (95% CI, 7.5–10.3 cases per 100 person-years), which is slightly higher than the 7.4 cases per 100 person-years (95% CI, 6.6–8.4 cases per 100 person-years) reported in the previously published analysis [2]. As predicted by Caluwaerts and Colebunders [1], this difference was more pronounced during the firs 3 months of treatment: 13.9 cases per 100 person-years (95% CI, 11.0–17.6 cases per 100 person-years) in this analysis, compared with 10.7 cases per 100 person-years (95% CI, 8.9–12.9 cases per 100 person-years) in the original analysis. The decrease in the incidence rate during the firs year of HAART was, however, similar for the 2 analyses. Compared with the rate for months 1–3, the rate ratio was 0.65 (95% CI, 0.44–0.96) for months 4–6 and was 0.39 (95% CI, 0.27–0.58) for months 7–12. The corresponding ratios from the original analysis were 0.70 (95% CI, 0.52–0.94) and 0.48 (95% CI, 0.36–0.64), respectively. Interestingly, the inci-

dence-rate ratios from this analysis are somewhat closer to those reported for the high-income cohorts in the original analysis [2]. The sensitivity analysis prompted by the letter from Caluwaerts and Colebunders thus strengthens our conclusions that the reduction in rates of TB during the firs year of HAART is similar in low-income and high-income settings.


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## References


1. Colebunders R, Caluwaerts S. Determination of the incidence of tuberculosis in low-income countries. Clin Infect Dis **2008**; 46:1482 (in this issue).
2. The Antiretroviral Therapy in Low-Income Countries Collaboration of the International epidemiological Databases to Evaluate AIDS (IeDEA) and The ART Cohort Collaboration. Tuberculosis after initiation of antiretroviral therapy in low-income and high-income countries. Clin Infect Dis **2007**; 45:1518–21.



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# Shock as a Covariate in a Study of Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

To the Editor—Although the recently published article by Soriano et al. [1] comments on an important and interesting topic, I feel that the article has significan methodological flaw that have an impact on the conclusions made by the authors. Specificall , there are large and important differences between the OR estimates from the multivariate and univariate analyses for the association of mortality and vancomycin treatment group (see table 1, which summarizes the ORs presented by Soriano et al. [1]). The authors placed shock as a covariate in their multivariable model. They give the rationalization that this is a negative confounder of the association between treatment group and mortality.

**Table 1. The association of vancomycin treatment group and OR of mortality.**

| Treatment group | OR | |
|---|---|---|
| | Univariate | Multivariable |
| VMIC 1.0 | 1.0 | 1.0 |
| VMIC 1.5 | 1.9 (0.8–5) | 2.9 (0.9–9.4) |
| VMIC 2.0 | 2.6 (0.9–8) | 6.4 (1.7–24.3) |
| NA | 2.3 (0.9–6) | 3.6 (1.2–10.9) |

**NOTE.** Data are summarized from the article by Soriano et al. [1]. NA, receipt of inappropriate empirical therapy; VMIC 1.0, receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1 μg/mL; VMIC 1.5, receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1.5 μg/mL; VMIC 2.0, receipt of empirical vancomycin and an isolate with a vancomycin MIC of 2 μg/mL.

I would argue, however, that shock should not be in the model, because it is on the causal pathway from treatment group to death. Including this in the model would generate OR estimates for the association of treatment group and mortality, which then are—theoretically—independent of shock.

I am not sure how to interpret their model in this context or the multivariable OR they present. What is the reason to include shock as a covariate?

It would be helpful to see a multivariable model for the association of treatment group and mortality without shock as a covariate in the model. It would also be helpful to see an assessment of the overall statistical significanc of the treatment-group effect in the model, in addition to the individual OR by subgroup.


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## Reference


1. Soriano A, Marco F, Martinez JA, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis **2008**; 46:193–200.



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# Vancomycin Minimum Inhibitory Concentration as a Predictor of Mortality in Methicillin-Resistant *Staphylococcus aureus* Bacteremia: A Second Look

To the Editor—We read with interest the article by Soriano et al. [1] that described vancomycin MIC as a predictor of mortality in patients with methicillin-resistant *Staphylococcus aureus* bacteremia. The issue of MIC "creep" was documented elsewhere [2], and the conclusion that a higher MIC is associated with an increased risk of mortality is not surprising. In addition, the presence of shock associated with methicillin-resistant *Staphylococcus aureus* bacteremia was documented elsewhere as a risk factor for mortality [3]. However, the negative association between the development of shock and vancomycin MIC is extremely intriguing. Soriano et al. [1] hypothesize that this relationship could be attributed to a decrease in pathogenicity as resistance increases through a variety of mechanisms. We offer an alternative explanation of the data and address some concerns with the study by Soriano et al. [1].

After examination of the absolute incidence of patient characteristics, it is clear that the development of shock is negatively associated with vancomycin MIC without adjustment for confounding variables (for 1 μg/mL, 28.4%; for 1.5 μg/mL, 20.2%; for 2 μg/mL, 10.9%; $P = .007$). It is also clear that heart failure occurred in a significantl higher percentage of pa-