a reflection of FSW clients' preferences for unprotected sex. These findings have several important implications for HIV prevention strategies among FSW. First, the size of risky sex premium is large enough that it may dampen the effectiveness of certain behavioral interventions to reduce STI and HIV risk among FSW, such as condom promotion efforts. Although condom promotion efforts have had much success among FSW[7] and a large proportion of FSW in our study also reported consistent condom use, the large risk premiums in combination with factors such as poverty may contribute to some FSW engaging in unprotected sex with clients. Second, cash transfers conditioned on avoiding STIs may serve as a way to directly address the implications of the risky sex premium, although the feasibility and scalability of such interventions need to be assessed. Third, biomedical interventions such as pre-exposure prophylaxis may be a promising strategy to reduce HIV infections among FSW because price premiums for unprotected sex are so large.

Comparing the size of the risky sex premium in our study setting to those estimated in other settings can be instructive. Estimates of premium vary widely in the literature, from a 23% premium in Mexico,[8] a 66%–79% price reduction for sex with condom in India,[9] 350% premium in the Demographic Republic of Congo,[10] and a 43% premium in rural Zimbabwe.[11] Another study in a different part of western Kenya has shown that formal and informal FSWs increased their supply of unprotected sex when coping with unexpected income shocks but found considerably smaller risk premium of only 9.3%.[12] The large premiums in our study setting could be due to the higher HIV prevalence in Kisumu, as disease risk is known to be an influential factor in determining the size of risky sex premiums.[13] Consistent with findings from other studies, more educated women were able to negotiate higher prices overall and a larger premium for unprotected sex than less educated women.[8,9,11] Education might enable women to negotiate prices that better compensate them for taking the extra risk of unprotected sex.

Limitations of this study include a small sample size of FSW who report prices of sex without condoms and the conduct of the study at only 1 site. We explored whether FSW who did not disclose a price for sex without condom differed from the rest of the sample but did not detect any differences in measured characteristics other than whether they always used a condom with clients. Additional data collection from a larger sample and across multiple sites can help assess the generalizability of the results and improve our understanding of the commercial sex market. Nonetheless, the consistency of our findings with other studies provides greater confidence in their validity.

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Performance of Risk Charts to Guide Targeted HIV Viral Load Monitoring of ART: Applying the Method on the Data From a Multicenter Study in Rural Lesotho

***To the Editors*:**

We read the article of Koller et al[1] on risk charts to guide targeted viral load (VL) monitoring with great interest. Although the World Health Organization (WHO) guidelines on the use of antiretroviral therapy (ART) published in 2013 recommend routine VL monitoring, its implementation remains slow in most countries in Sub-Saharan

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Africa.[2,3] In settings with limited laboratory capacity for VL monitoring, tools that help to identify the group of patients who most need VL testing may provide an alternative until HIV programs are capacitated to implement routine VL monitoring. Ideally such tools help to sort out patients who are highly likely to have virologic failure and those who are very unlikely to fail, narrowing down the number of patients receiving VL to those who are at intermediate risk. WHO immunological and clinical criteria perform poorly in predicting as well as excluding virologic failure.[4] Scores based on clinical and laboratory parameters for identifying those who need targeted VL had acceptable accuracy in some settings,[5,6] but not in others.[7]

Based on the analysis of 7 South African cohorts including more than 30,000 patients, Koller et al propose the use of risk charts based on basic pieces of information: sex, time on ART, baseline, and current CD4 counts. The charts allow one to exclude patients with very high or very low probability of virologic failure, restricting VL testing only to those with intermediate probability of failure. In a setting where limited resources are available, the charts help to optimize VL testing to those patients with the highest uncertainty on virologic outcome (10%, 20%, or 40% of a cohort, depending on the VL tests available).

Here we report performance of the risk charts published by Koller et al on data that had been collected as part of a prospective study on virologic outcomes and comorbidities in 10 rural clinics in Lesotho, Southern Africa [Comorbidities and Virologic Outcome Among Patients on Anti-retroviral Therapy in Rural Lesotho (CART)-1 www.clinicalTrials.gov ID: NCT02126696]. Between May 5, 2014 and June 17, 2014, we assessed VL in patients on first-line ART ≥6 months in 10 clinics located in 2 rural districts of Lesotho. The study has been described in more detail elsewhere.[7]

Patients with a plasma VL ≥1000 copies per milliliter can resuppress spontaneously or after increased treatment adherence.[8] To avoid unnecessary switching to a second-line regimen, WHO therefore recommends a second VL measurement after 3 months of enhanced adherence support and switch to second line if second VL remains ≥1000 copies per milliliter.[2,8] In accordance with these guidelines, our study measured a first VL in all participants with a follow-up VL 3 months later for those with an elevated first VL. Following the method of Koller et al, we assessed performance of the risk charts in predicting single virologic failure (first VL ≥1000 copies per milliliter) and sustained virologic failure (first and follow-up VL ≥1000 copies per milliliter), as a function of time on ART, CD4 at baseline, current CD4, and sex.

The statistical analysis used 2 methods:

- Method 1: we straightforwardly applied the boundaries for CD4-cell values defined in Figure 1 of the article of Koller et al.[1] This method implies that the percentage of patients qualifying for VL testing may differ from cohort to cohort and deviate from the targeted values (10%, 20%, or 40%).
- Method 2: we focused on the targeted values of proportions of patients who shall receive VL testing (10%, 20%, or 40%). To achieve this objective, we took the values from the central line in Figure 1 from Koller et al and then increased or decreased progressively the interval widths till the targeted proportion of the patients qualifying for VL testing in our cohort was reached.

Koller et al elaborated the risk charts for patients on ART <5 years. Because approximately one-third of our study population had been on ART ≥5 years, we assessed in an additional analysis the robustness of the method including patients on ART >5 years, applying the boundary values at year 5.

To retrieve the lines plotted in Figure 1 of Koller et al, we took 10 points of measurement and then proceeded with linear interpolation. All

TABLE 1. Measures of performance of Methods 1 and 2.

n = 905	0% VL Testing		10% VL Testing		20% VL Testing		40% VL Testing	
Virologic Failure*	**Single**	**Sustained**	**Single**	**Sustained**	**Single**	**Sustained**	**Single**	**Sustained**
Method 1								
n VL test (%)	0		58 (6.4)		113 (12.5)		222 (24.5)	
PPV†	42	28	67	46	81	54	89	62
NPV‡	96	97	97	98	97	98	97	98
Sensitivity	33	32	47	49	54	54	60	62
Specificity	97	96	98	98	99	98	99	98
Method 2								
n VL test (%)	0		92 (10.2)		183 (20.2)		365 (40.3)	
PPV	42	28	78	53	94	64	100	67
NPV	96	97	97	98	97	98	98	99
Sensitivity	33	32	51	51	56	57	71	70
Specificity	97	96	99	98	100	99	100	99

*Single virologic failure: first VL ≥1000 copies per milliliter; sustained virologic failure: first and follow-up VL ≥1000 copies per milliter.
†Positive predictive value.
‡Negative predictive value.
NPV, negative predictive value.

analyses were run on R 3.2.2 (the R Foundation for Statistical Computing), and TIBCO Spotfire S+ 8.1 for Windows (TIBCO Software Inc).

Among 1563 adults on first-line ART ≥6 months enrolled in the study, 1404 had both documented baseline and current CD4 values. There were 69% women, the median age was 44 years (interquartile range 35–54), and the median CD4 count at start of ART was 215 cells per cubic millimeter (interquartile range 122–306). Among them, 905 (64%) had been on ART 6 months to 5 years, the remaining 499 patients had been on ART >5 years.

Results are shown in Table 1. Applying method 1, using fixed CD4-value boundaries, fewer patients qualified for VL testing than in the article of Koller et al (6.4% in the 10% boundaries; 24.5% in the 40% boundaries). Taking a first VL ≥1000 copies per milliliter as reference, the positive predictive value (PPV) increased from 67% (10% boundaries) to 89% (40% boundaries), and the corresponding sensitivity from 47% to 60%.

Method 2, using a fixed targeted percentage to receive VL testing, resulted in larger CD4-value intervals than in the article of Koller et al. Taking a first VL ≥1000 copies per milliliter as reference, the PPV increased from 78% (10% tested) to 100% (40% tested), and the corresponding sensitivity from 51% to 71%. All the estimates that we obtained with method 2 fell between the range of values obtained by Koller et al, or better. If a sustained virologic failure was taken as a reference (2 VL ≥1000 copies per milliliter; ≥3 months apart), the PPV would decrease by up to 30%, whereas the sensitivity would remain stable or slightly increase.

We also tried to include those patients on ART >5 years as if they had been on ART for 5 years. This did not change results substantially: differences were at maximum of 7%, 6%, and 4%, with, respectively, 10%, 20%, and 40% of VL testing.

In the same patient-cohort WHO-proposed immunological criteria for treatment failure[2] had a sensitivity of 16% and a PPV of 56% for a single VL ≥1000 copies per milliliter and a sensitivity and PPV for sustained virologic failure of 22% and 50%, respectively.

Several groups elaborated algorithms using clinical and laboratory information to predict virologic outcomes among patients on first-line ART. Liu et al[9] developed an algorithm based on CD4 values and simple clinical markers. Tested in a data set from a US patient cohort, this approach had high accuracy in predicting VL ≥400 copies per milliliter. It has to our knowledge, however, not been validated in resource-limited settings. Evans et al[10] developed a score using a variety of clinical and laboratory variables at baseline and follow-up. This score had high accuracy. It, however, includes laboratory values, such as mean cell volume and albumin, which are usually not part of routine laboratory follow-up in resource-constrained settings. Based on data from a cohort on first-line ART in Cambodia, Lynen et al[5] developed a clinical prediction score, including CD4 count, change in hemoglobin, drug adherence, and presence of papular pruritic eruption. Whereas the score performed well in Cambodia[11] and Lesotho,[6] it had very poor accuracy in Uganda.[12] All these approaches require reliably documented clinical and laboratory history that may not implicitly be available in resource-limited settings. Van Griensven et al[13] assessed simplified scores that do not require hemoglobin measurement and no baseline CD4 count. These scores had a still acceptable accuracy in a Cambodian cohort.

A strength of the risk charts of Koller et al is that they only require a baseline and a current CD4 count. Poor documentation of additional laboratory values or clinical history is a reality in many resource-limited settings.

Adherence measurement, such as pill count during pharmacy refill, does not require specific equipment, is relatively cheap, and was predictive of virologic outcome in several studies.[14–16] It was, however, not associated with virologic failure in the CART-1 study, the data set we used for this analysis.[17]

Implementation of the risk charts developed by Koller et al would mean that health care providers possess charts adapted to their context. At each visit where patients on first-line ART obtain a CD4 count result, HIV care providers could check on these charts if the patient falls into the intermediate risk group and decide if a VL is indicated. To do so, the provider only needs 4 variables: sex, time on ART, CD4 count at baseline, and current CD4 count. Such a scenario seems realistic and feasible—even in very resource-limited settings, such as Lesotho, where HIV care has been shifted to nurses. It may be much more realistic than more complex algorithms and scores that require technology or information that may not be available or adherence measurements that are prone to interobserver variability.

In conclusion, in this multicenter cohort from rural Lesotho, the CD4-risk charts performed at least as well, if not better, than in the original article of Koller et al and substantially better than the WHO criteria for immunological failure. Risk charts may be of particular interest to settings that start VL testing, but where resources do not allow routine VL monitoring for all patients yet. Before implementation at a larger scale, their accuracy for sustained virologic failure that would eventually trigger switch to second-line ART should be further examined.

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