Is Tenofovir-Related Renal Toxicity Incompletely Reversible?

To the Editors:

Wever et al[1] report "incomplete reversibility of tenofovir (TDF)-related renal toxicity in HIV-infected men". The authors' report highlights that TDF-related renal toxicity may not always be fully reversible, particularly in those with gradual decline in estimated glomerular filtration rate (eGFR). The study describes 24 patients who ceased TDF for suspected renal toxicity and compared serum creatinine with eGFR (Cockcroft-Gault and Modification of Diet in Renal Disease) before initiating TDF, at the time of stopping TDF, and the most improved value after stopping TDF. The median age of the patients was 56 years, the median duration of TDF exposure 30 months, the median eGFR at TDF initiation 74 ml·min^{-1}·1.73 m^{-2}, and most patients received protease inhibitors and had good virological control. At the time of TDF discontinuation, the eGFR (Modification of Diet in Renal Disease) had declined to 51, with subsequently improvement to 64 ml·min^{-1}·1.73 m^{-2} (most improved value) and 58 ml·min^{-1}·1.73 m^{-2} (most recent measurement). The authors conclude that TDF-associated renal toxicity was not fully reversible in 58% of subjects. Although this may be correct, it should be appreciated that many patients with reduced eGFR (<90 or <75 ml·min^{-1}·1.73 m^{-2}) may have underlying chronic kidney disease, the natural history of which may be progressive in nature. Consequently, over a 3-year period (30 months of TDF exposure and 5 months of recovery), eGFR declines that are observed in the setting of drug-induced renal injury may not recover fully after drug discontinuation when the underlying renal disease has progressed during this time. This would be more likely if drug exposure has been prolonged and if drug-induced kidney injury was insidious in onset. We propose that eGFR slopes may provide better insight into the potential reversibility of TDF-associated nephrotoxicity, as they allow estimation of the rate of CKD progression before TDF initiation, during TDF exposure, and after TDF discontinuation.

TABLE 1. eGFR Slopes in Patients With and Without CKD (eGFR <60 ml·min^{-1}·1.73 m^{-2} for >3 Months)

eGFR Slopes	Before TDF Initiation	During TDF Use	Following TDF Discontinuation
Patients who developed CKD	−2.3 (−3.2 to −1.4)	−8.5 (−9.4 to −7.6)	−2.2 (−6.6 to +2.1)
Patients without CKD	+1.2 (+1.1 to +1.4)	−0.8 (−1.1 to +0.2)	+3.9 (+2.1 to +5.1)

We analyzed renal function using eGFR slopes in 843 patients who initiated TDF-containing cART, and of whom 26 (3.1%) developed CKD (defined as an eGFR <60 ml·min^{-1}·1.73 m^{-2} for >3 months). Compared with patients who did not develop CKD, those who developed CKD were older (53.6 vs 39.9 years, $P < 0.001$) and had significantly lower eGFR at TDF initiation (69 vs 102 ml per minute, $P < 0.001$). In addition, 85% had other risk factors for CKD progression including underlying cardiovascular disease or exposure to other potentially nephrotoxic drugs.[2] When changes in renal function over time were examined, patients who developed CKD already experienced modest eGFR decline (−2.3 ml·min^{-1}·year^{-1}) before TDF initiation. Accelerated decline in eGFR (median –8.5 ml·min^{-1}·year^{-1}) was observed during TDF exposure, with subsequent return to the pre-TDF eGFR slope of –2.2 ml·min^{-1}·year^{-1} after TDF discontinuation. In patients who did not develop CKD, a similar, but much more modest decline in eGFR was observed (Table 1).

Even though our data suggest that TDF-related renal toxicity may be largely reversible, it clearly is best avoided by monitoring changes in renal function over time. Although the optimal frequency of monitoring is unknown, the modest rate of renal disease progression in patients on TDF would support annual or biannual assessment of renal function. Although we agree with Wever et al[1] that an eGFR >60 ml·min^{-1}·1.73 m^{-2} may lead to consideration of TDF discontinuation, it may be important to identify those at greatest risk of TDF-associated renal toxicity, including those aged >50 (odds ratio: 5.4) and patients who have eGFR <75 ml·min^{-1}·1.73 m^{-2} at TDF initiation (odds ratio: 17.2),[2] and either avoid TDF if suitable alternatives are available, or use TDF with more close monitoring of renal function.

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eGFR Slope and Tenofovir Nephrotoxicity

To the Editors:

We thank Campbell et al for their evaluation of our hypothesis that

tenofovir-related nephrotoxicity is not always fully reversible. They correctly note that we did not report the rate of decline in estimated glomerular filtration rate (eGFR) before initiation of tenofovir. They state that tenofovir-related nephrotoxicity is reversible because the decline in eGFR in those who developed chronic kidney disease (eGFR <60 mL $min^{-1}{\cdot}1.73\ m^{-2}$ for at least 3 months) was similar before tenofovir initiation and after tenofovir cessation (-2.3 mL $min^{-1}{\cdot}1.73\ m^{-2}$ per year and -2.2 mL $min^{-1}{\cdot}1.73\ m^{-2}$ per year, respectively).

However, the rate of change after tenofovir discontinuation will be the sum of the rate due to pre-existing renal disease and of the rate of recovery from tenofovir toxicity. If tenofovir-related nephrotoxicity were reversible, the rate of change after tenofovir cessation must be less (ie, more positive) than the rate before cessation, as the underlying rate of decline associated with pre-existing renal disease would necessarily be lessened by any increase in eGFR after tenofovir cessation. For example, if eGFR declined by 2.3 mL $min^{-1}{\cdot}1.73\ m^{-2}$ per year before tenofovir, then declined by 8 mL $min^{-1}{\cdot}1.73\ m^{-2}$ per year on tenofovir and then fully reversed, then the rate of change after tenofovir cessation would be about +5.73 mL $min^{-1}{\cdot}1.73\ m^{-2}$ per year. The similar rates before and after tenofovir therapy in the population described by Campbell et al suggest that tenofovir nephrotoxicity was, as in our patients, also not reversible in those who developed chronic kidney disease.

Our interpretation of these new data is that tenofovir nephrotoxicity does not progress when tenofovir is stopped but that tenofovir nephrotoxicity is not fully reversible.

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Detrimental Effect of Atazanavir Plasma Concentrations on Total Serum Bilirubin Levels in the Presence of UGT1A1 Polymorphisms

To the Editors:

Atazanavir (ATV), a protease inhibitor of HIV, acts as an inhibitor of the UDP-glucuronosyltransferase (UGT)1A1, an enzyme responsible for bilirubin metabolism, leading to unconjugated hyperbilirubinemia.[1] The frequency and the severity of hyperbilirubinemia correlates with the UGT1A1 gene polymorphisms, mimicking the mechanism underlying Gilbert Syndrome.[2,3] Furthermore, bilirubin levels directly correlate with ATV plasma concentrations.[3,4] To our knowledge, the interaction between ATV plasma concentrations and the UGT1A1 polymorphism has never been formally tested, assuming their effects to be additive. The aim of this study is to assess whether the impact of ATV plasma concentrations on serum bilirubin was different according to the presence of UGT1A1-TA_7 allele.

Patients cared at our Institute treated with ATV 300 mg plus ritonavir 100 mg (ATV/r) and 2 nucleoside analogues for longer than 3 months were identified. Plasma ATV concentration was measured after 24 ± 4 hours drug intake [trough concentration (C_{trough})] by a validated high-performance liquid chromatography method.[5] Genetic profile of the UGT1A1 gene was assessed by direct sequencing of DNA extracted from peripheral blood mononuclear cell.[6]

Descriptive results of continuous variables were expressed as median and interquartile range (IQR) values. Univariate and multivariate linear regression models were used to investigate factors correlated with total serum bilirubin. Sixteen of 55 patients (29.1%) were female, the median age was 43 years (IQR 39–49), and the body mass index (BMI) was 23.7 (IQR 21.8–25.5). The CD4 cell count was 468 cells per microliter (IQR 336–588). The median follow-up on ATV was 14.5 months (IQR 5–32). The median serum bilirubin was 2.53 mg/dL (IQR 1.31–3.94), and the proportion of patients with grade 3 (>2.5 × Upper Normal Limit [ULN]) and grade 4 (>5 × ULN) hyperbilirubinemia was 50.1% and 12.7%, respectively. The median ATV C_{trough} was 1 mg/L (IQR 1–3). The distribution of UGT1A1 genotypes was as follows: TA_6/TA_6 in 43.6%, TA_7/TA_6 n 40%, TA_7/TA_7 in 16.4%. The median bilirubin level in each genotype was: 2.1 mg/dL (IQR 1.2–2.8) in TA_6/TA_6, 2.58 mg/dL (IQR 1.3–3.9) in TA_6/TA_7, 5.2 mg/dL (IQR 3.0–7.6) in TA_7/TA_7 ($P = 0.05$). There were no significant differences between the 3 genotypes in terms of age, gender, BMI, CD4 count, and ATV plasma level. When total serum bilirubin was regressed on ATV plasma concentration and UGT1A1 polymorphism, the expected difference in total bilirubin resulted: 1.49 (SE 0.38; $P = 0.0003$) per unit difference in ATV C_{trough}, and increased of 1.39 factor (SE 0.51; $P = 0.0009$) if at least 1 UGT1A1-TA_7 allele was present ($rho^2 = 0.26$). To test whether the difference in total bilirubin per unit difference in ATV plasma concentrations changed according to the presence of the UGT1A1-TA_7 allele, a polymorphism-by-ATV C_{trough} interaction term was included in the model. The increase in total bilirubin per unit difference in ATV C_{trough} resulted 0.80 (SE 0.39) in patients with TA_6/TA_6 genotype and 2.33 (SE 0.64) in patients carrying at least one TA_7 allele ($rho^2 = 0.29$; P for interaction = 0.04). The model did not change after adjusting for age, gender, CD4 count, and BMI. In addition, older age resulted independently correlated serum bilirubin level (Table 1).

The above results confirm a direct correlation between ATV plasma level and bilirubinemia that was influenced by the presence of homozygosis or heterozygosis for UGT1A1-TA_7 allele. Other authors concluded that severe hyperbilirubinemia was further increased by the presence of the UGT1A1-TA_7 allele,[3] however, to the best of our knowledge, this is the first study that formally tested the interaction between

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TABLE 1. Variation in Total Bilirubin Plasma Level Per Unit Difference in ATV Plasma Trough Concentrations According to the Presence of the UGT1A1-TA7 Allele: Results Form Linear Regression Models

	Unadjusted Model*		Adjusted Model†	
Predictor	**β (SE)**	***P***	**β (SE)**	***P***
ATV *C*truogh				
TA6/TA6	+0.80 (0.39)	0.04‡	+1.02 (0.40)	0.08‡
TA7/TA6-7	+2.33 (0.64)		+2.30 (0.62)	
Female gender	—	—	−0.31 (0.56)	0.58
Age (1 year older)	—	—	+0.05 (0.02)	0.05
BMI (1 additional unit)	—	—	−0.07 (0.05)	0.16
CD4 (every additional 100 cell/μL)	—	—	−0.03 (0.13)	0.78

*Total serum bilirubin regressed on ATV *C*truogh ATV, UGT1A1 polymorphism and polymorphism-by-ATV *C*trough interaction term.

†Same model as above adjusted for gender, age, BMI, and CD4 count.

‡The *P* value for interaction.

these 2 major predictors of hyperbilirubinemia in patients treated with ATV. In particular, carrying UGT1A1- TA_7 polymorphism accounted for a 2-fold increase in bilirubin level for a unit change in ATV plasma concentration (Table 1). In keeping with literature findings,[5,7] severe hyperbilirubinemia and hepatic toxicity were rare in our study population; only 2 patients showed increased (>2.5 times ULN) liver transaminase leading to interpret the herein observed hyperbilirubinemia as an innocent phenomenon (data not shown). Indeed, bilirubinemia and/or transaminase increases may not be frequently detected in patients on stable therapy, given that premature drug discontinuation occurs in subjects nontolerating the compound. The key question is: would UGT1A1 testing be cost-effective in the presence of an apparently innocent side effect?

The occurrence of jaundice may be considered undesirable by some patients, thus limiting adherence to ATV and increasing the probability of treatment failure. Furthermore, studies linked the reduced glucuronidation activity in the presence of the TA_7 allele, to cancer disposition[8] and severe unwanted drug reactions.[9] ATV, acting as an inhibitor of UGT proteins, might enhance these effects particularly in individuals who already suffer from reduced UGT activity. Findings that better characterize the interaction between ATV plasma concentration and serum bilirubin may help in dose adjustments under the guidance of therapeutic drug monitoring. In general, haplotype identification as pharmacogenomic risk factors might improve drug safety and establish individualized pharmacotherapy.

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Clinical Impact and Cost of Laboratory Monitoring Need Review Even in Resource-Rich Setting

To the Editors:

Multiple studies have demonstrated the relatively low clinical impact and cost of frequent laboratory monitoring of asymptomatic patients receiving antiretroviral therapy (ART) in resource-poor settings.[1,2] We propose taking these conclusions a step further into resource-rich settings given the rising cost of healthcare.

The costs for treatment and medical care of an HIV-positive individual in the United States are as high as $34,000 per year with estimated lifetime costs surpassing 1 million dollars per patient.[3] Furthermore, it is anticipated that the number of patients on ART, the time on therapy, and the commensurate costs will continue to increase.[4–10] Given this rising number, it is critical that evidence based on best practices with regard to efficacy, safety, and cost-effectiveness is employed in the treatment of HIV. Current HIV treatment guidelines recommend that routine laboratory monitoring should be conducted every 3 months to monitor treatment effects, virologic breakthroughs, and timely detection of toxicities.[8] However, with the advent of newer more efficacious ARTs with reduced toxicities, these older recommendations need to be re-evaluated.

We conducted a retrospective cohort study of existing medical record

TABLE 1. Demographic and Clinical Characteristics of Patients Seen Quarterly as Compared With Patients Seen Semiannually, AIDS Healthcare Foundation, Los Angeles, CA, September 1, 2008, to September 1, 2009

	Quarterly Testing (n = 513)	Semiannual Testing (n = 333)	*P*
Age, mean (SD)	45.9 (9.7)	44.3 (9.1)	< .01
Gender, n (%)			
Male	433 (84.4)	304 (91.3)	0.16
Female	65 (12.7)	25 (7.5)	
Transgender	15 (2.9)	4 (1.2)	
Race/ethnicity, n (%)			
African American	73 (14.2)	74 (22.2)	0.44
Asian	16 (3.1)	11 (3.3)	
Hispanic	266 (51.8)	143 (42.9)	
White	154 (30.0)	104 (31.2)	
Other	4 (0.8)	1 (0.3)	
$CD4^+$ cells/ul, mean (SD)			
Initial test	578 (285)	555 (266)	0.21
Follow-up test at 6-months	607 (290)	561 (266)	—
Difference (Follow-up test - Initial test)	29 (6.4)	6 (8.2)	0.03
P value for difference*	< 0.01	0.47	—
HIV-1 RNA levels (log10 copies/ml), mean (SD)			
Initial test	1.84 (0.6)	2.11 (0.9)	0.10
Follow-up test at 6 months	1.82 (0.5)	2.07 (0.5)	—
Difference (Follow-up test - Initial test)	−0.02 (0.5)	−0.04 (0.8)	0.65
P value for difference*	0.31	0.34	—

*The *P* value based on a *t* test.

data in our Southern California clinics to evaluate differences in HIV-1 RNA levels and $CD4^+$ cell counts of patients seen every 3 months as compared with those seen every 6 months. We selected records for inclusion in this analysis if the patient had (1) been on antiretroviral therapy for at least 3 months before data extraction, (2) >95% adherence to ARTs, and (3) had routine $CD4^+$ cell counts and HIV-1 RNA levels checked either at 3-month or at 6-month intervals. We selected patients with high adherence to limit potential confounding effects of adherence on the biomarkers of interest.

Between September 1, 2008, and September 1, 2009, a total of 846 eligible patients were identified and included in our analysis. We found no differences in terms of gender, race/ethnicity, baseline $CD4^+$ cell counts, and HIV-RNA levels between those who were seen at regularly scheduled 3-month follow-up visits as compared with those who had a 6-month follow-up visit (Table 1). No differences were noted in HIV-1 RNA levels at follow-up (*P* value = 0.65), however, clinically minimal though statistically significant improvements were noted in $CD4^+$ cell counts (29 cells/uL vs. 6 cells/uL; *P* = 0.03).

One of the critical questions regarding antiretroviral therapy management is what constitutes optimal monitoring, and clearly this issue has implications for resources allocation. Evidence should guide policies for laboratory monitoring, especially if data shows that this may not be a good use of resources. Nationally, there is a need for a randomized prospective study evaluating the safety of limited laboratory monitoring in stable patients on ART to demonstrate if this is a good use of resources in a time of dwindling health care dollars.

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Probiotics: The Potential for a Live Microbicide to Prevent HIV

To the Editors:

INTRODUCTION

After early microbicide candidates failed in clinical trials to prevent HIV,

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Presented at Satellite Symposium titled 'Probiotics: the Potential for a Live Microbicide' at Microbicides 2010; Pittsburgh, PA.

recent news from the South African CAPRISA-004 study suggest that the new generation of vaginal microbicide gels using antiretroviral drugs like tenofovir could be effective and reduce HIV and herpes simplex virus-2 acquisition.[1] This landmark study greatly energized the field and revived enthusiasm for the development of female-controlled products to prevent HIV acquisition in women, and if ongoing trials confirm the CAPRISA-004, results lead to a licensed product by 2014.[2,3]

Although the field is getting closer to identifying an effective compound against vaginal HIV transmission, significant challenges remain, such as a sustained coitally independent release of an effective drug and a product formulation and administration that suits life circumstances of women in developing countries. Stigma continues to limit women's access to HIV prevention strategies, and many women underestimate their own risk of HIV infection.[4] Thus, a microbicide product perceived to improve overall vaginal health may decrease possible acceptability barriers that a single purpose product associated with HIV prevention may face.

In late May, the biannual global conference Microbicides 2010 held in Pittsburgh, PA, was attended by 1000 scientists and advocates, including more than 300 from Africa. The UCSF Bixby Center for Global Reproductive Health and the Consortium to Advance Multipurpose Innovations organized a Satellite Symposium titled "Probiotics: the Potential for a Live Microbicide". The event provided a platform for researchers working in related fields to educate the conference audience and to initiate a discussion with other scientists, donors, advocates, members of federal agencies and world bodies, and regulatory experts to accelerate the development of probiotics for HIV prevention.

A handful of small biotechnology companies and academic groups are working to develop a new generation of genetically enhanced probiotics by inserting genes which code for potent antiviral compounds into bacteria that naturally colonize the vagina. Once administered to the vagina, these next generation probiotics have the potential to serve as a sustained, self-replicating delivery system for antimicrobial compounds to combat reproductive tract infections, including HIV. The potential advantages of a probiotic microbicide continuously producing anti-HIV protein compounds *in situ* over conventional microbicide delivery systems such as gels and films include (1) periodic, possibly weekly or monthly replenishment versus coitally dependent or daily dosing; (2) minimal disposal concerns, for example applicators; and (3) low risk of developing HIV resistance in comparison to antiretroviral therapy commonly used in treatment, such as tenofovir.

However, the field to date has been hampered by a relative lack of interest among donors due to competing HIV prevention technologies under development, lack of clarity regarding the regulatory pathway for licensure and general sensitivity surrounding genetically modified organisms (GMO), and financial fall-out from the recent worldwide recession.

PROBIOTIC MICROBICIDES FOR HIV PREVENTION

The normal vaginal environment is dominated by self-replicating lactobacilli species that maintain an acidic pH and inhibit the growth of pathogens and subsequent infections. Research of probiotic lactobacilli to improve genital health has increased steadily over the last 2 decades. The first generation of probiotics uses selected human strains for the prevention of recurrent bacterial vaginosis (BV) and urinary tract infection (UTI) following standard antibiotic treatment. Over time, researchers in this field have utilized new diagnostic technology such as rDNA polymerase chain reaction and improved product formulations and dosing regimens. Clinical trials have successfully demonstrated vaginal colonization with exogenous *Lactobacillus* strains and provided data on effectiveness against recurrent BV[5–8] and UTI.[9] Advances of these products will likely require testing of additional approaches, such as extending antibiotic treatment to more effectively destroy the bacterial biofilm and overcoming the negative influence of semen exposure[10] and menstruation on the proportion of women colonized with the exogenous *Lactobacillus* strains.

The next generation of probiotics will be genetically engineered. Highly potent HIV inhibitors can be continuously produced by genetically enhanced self-renewing *Lactobacillus* bacteria that colonize the vaginal mucosa after periodical vaginal application.

The genetically modified *Lactobacillus jensenii* 1153-1666 (MucoCept) developed by Osel, Inc. follows this approach. Naturally occurring vaginal *Lactobacillus* strains were evaluated, and the *L. jensenii* 1153 was selected as the single best strain. Next, this strain was engineered to produce the potent HIV entry inhibitor Cyanovirin-N (CV-N). Last, Osel developed technology to preserve large quantities of MucoCept as a freeze-dried stable powder of pharmaceutical grade quality.

The further development of next generation probiotics will require extensive preclinical and early clinical testing before their efficacy can be tested. To be effective, these bacteria need to colonize the vagina in high concentrations in a large majority of women. In addition, the *in situ* protein expression and bioactivity and the immunological responses of the host need to be carefully monitored. Experiments in 20 Chinese rhesus macaques showed consistent lactobacilli colonization of CV-N-expressing *L. jensenii* for up to 90 days, at high levels of 10^5–10^7 colony-forming units (CFU) per swab.

In theory, because the CV-N protein is "foreign", and the *L. jensenii* is not native to the macaque, an antibody response to either the CV-N or to the lactobacilli is possible, rendering the molecule inactive as a microbicide. During regular tests, using enzyme-linked immunosorbent assay in macaques exposed for more than 6 months, no antibody response to either the recombinant CV-N or to *L. jensenii* has been found in blood or cervicovaginal lavage samples (Dr. Qiang Xu, PhD, personal communication, 2010). Furthermore, the strain was easily cleared by topical administration of azithromycin.

In a repeated low-dose challenge model, Chinese rhesus macaques receiving MucoCept in comparison to controls had a 62% reduction in the rate of simian HIV acquisition ($P = 0.037$) (Dr. Laurel Lagenaur, PhD, personal communication, 2010). Next steps for the development of this product include a prephase 1 clinical trial of MucoCept to evaluate colonization, clearance after antibiotic treatment and

biocontainment in a small group of healthy volunteers. In addition, Osel is exploring MucoCept as a platform to coexpress additional HIV inhibitors for as a multipurpose microbicide against HIV and other sexually transmitted infections (STIs).

Other groups of researchers are exploring similar concepts. ActoGenix, a Belgian company, is using genetically modified *Lactococcus lactis*, derived from the food industry, as a platform to deliver proteins such as the antiinflammatory cytokine Interleukin-10 to downregulate inflammatory bowel disease and ulcerative colitis. A *L. lactis*–producing Trefoil Factor 1 has been designed to prevent colitis[11] and oral mucositis,[12] a debilitating and painful side effect of radiotherapy and chemotherapy. Clinical phase 2 studies are under way for these products, and ActoGenix is also exploring *L. lactis* as a safe platform to deliver proinsulin to treat juvenile diabetes.

Due to the mixed perception and consideration of testing GMO in different regions of the world and to increase donor support to develop these products, the field needs to educate key stakeholders including the regulatory agencies around the world. The regulatory approval process for probiotic drugs faces unique challenges. First, in contrast to probiotic foods, pharmaceutical grade drugs need to be produced in facilities complying with Good Manufacturing Practices. Second, drugs that are deliberately releasing GMO need to follow country-specific guidelines addressing biocontainment and eradication. Third, regulatory agencies in different countries may have unique requirements that need to be sufficiently and proactively addressed when planning for and designing future clinical studies.

Although women in sub-Saharan Africa have the highest need for female-controlled HIV prevention technologies, women in other regions also require better prevention tools against HIV and other STIs. In tandem with the scientific development of these drugs, scientists and companies should concern themselves with the different contexts in which this technology may be introduced. End-user communities need to be involved from the beginning to create awareness and ensure their support and input for the clinical research and the eventual marketing and distribution. In addition to potential users, other gate keepers like their male partners, community leaders, and health care providers need to be engaged. Importantly, the daily realities of end-users such as storage, sanitary requirements, disposal options, and cost need to be considered to ensure that probiotic microbicides proven effective for HIV prevention will be used.

CONCLUSIONS

The CAPRISA-004 results restored enthusiasm for microbicides as a key technology to prevent HIV. To fulfill the promise of microbicides, research for additional antiretroviral compounds and delivery mechanisms needs to be stepped up. Women are waiting for safe, easy to use, inexpensive, and efficacious technologies to help them prevent HIV and other STIs. Probiotics, as a potential live microbicide, offer significant advantages including their safety profile, and a simplified self-replicating drug delivery platform. In addition, probiotics could serve as a component of multipurpose prevention tools for sexual and reproductive health to prevent multiple adverse health outcomes simultaneously, including HIV, STIs, unplanned pregnancy, and other reproductive tract infections such as BV.

As a new technology, the development of enhanced probiotics as HIV prevention drugs faces complex and unique challenges including competition for financial support, regulatory hurdles, manufacturing and logistical barriers, and effective branding and commercialization. To overcome these barriers, it is critical to forge multidisciplinary alliances of scientists, advocates, funders, government agencies, regulators, health care providers, and community of end-users. We will need to build strong alliances to create the momentum to successfully move live microbicides from the laboratory to the community.

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Implications of the Henan Province Report on the Treatment as Prevention Debate

To the Editors:

Wang et al[1] provide retrospective data regarding highly active antiretroviral therapy coverage, HIV incidence, and behavioral, clinical, and quality-of-life risk factors for HIV transmission among serodiscordant couples from Henan Province, China.[1] The study found that HIV seroconversion rates were generally low over time. HIV seroconversion was associated with not always using condoms, having sexual activity 4 or more times per month, not switching antiretroviral treatment regimens, and having a high quality-of-life score on the psychological domain. Use of antiretroviral therapy by the seropositive member of the couple was not found to be protective against HIV seroconversion.

Although these findings are reaffirming of how psychological and sexual behaviours are implicated in seroconversion, they do not add meaningfully to the discussion regarding the role of antiretroviral treatment as prevention. We are surprised that this is not highlighted in the accompanying editorial.[2] Quite simply, and as acknowledged by Wang et al,[1] HIV transmission is directly associated with the level of virus present in the HIV-positive partner,[3] and they are unable to assess this relationship in this analysis, as they do not have data on longitudinal plasma HIV-1 virel load. As they note in the discussion, they do not even have data on adherence levels among those on therapy. Furthermore, the relationship described in this study between seroconversion and not switching antiretroviral treatment suggests that virological failure may indeed be playing an important role as a driver of HIV transmission. Complete monitoring of relevant variables, most critically plasma viral load, is essential to address the relationship between antiretroviral therapy coverage and HIV transmission.[4–8]

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HIV Treatment as Prevention: In the Real World the Details Matter

To the Editors:

Antiretroviral therapy (ART) certainly has the potential to reduce HIV transmission, and the use of treatment as prevention is highly desirable.[1] But the magnitude and durabilty of benefit of ART for prevention are unknown, and the provocative observational[2] and ecological studies[3,4] cited in Dr Montaner's and Hogg's correspondence do not offer such insight. We need to address 2 crucial issues as follows: (1) How should we advise HIV discordant couples about their transmission risk when the infected partner is receiving ART? (2) How do we develop a "test and treat" strategy" that reliably reduces incident cases of HIV.

Dr Wang Lu's article[5] is important because it reflects on both of the above questions in the real world, not as the result of a controlled study or a modeling exercise. Her detection of HIV transmission from people provided ART does not negate the idea that lowering the viral load could reduce the per-contact probability of an HIV transmission event[6]; this is not an idea in dispute. But in the real world—for many reasons—people do not always experience continued and reliable suppression of HIV with ART (even in China where treatment and care are free). In the real world, people cannot monitor their viral load and STDs before sexual encounters; and suppression of HIV in blood frequently fails to prevent HIV replication and shedding in the genital tract.[7]

The success of the "test and treat strategy" requires that ART provided under real-world conditions—like in rural China or rural Africa—reliably and durably prevent transmission of HIV with reduction in new cases of HIV; Dr Wang Lu report highlights the obvious challenges we face as we try to harness ART as an HIV prevention modality.

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Retention Among Adults Initiating Antiretroviral Therapy in South Africa: 2002–2007

To the Editors:

We read with interest the recent article "Trends in Retention on Antiretroviral Therapy in National Programs in Low-Income and Middle-Income Countries".[1] We agree that there is an urgent need for accurate data on the outcomes of patients on treatment, particularly as large antiretroviral therapy (ART) programs continue to scale-up services. As noted in the article, South Africa—with the highest number of people living with HIV and the largest ART program worldwide[2]—did not report on program retention.

We have recently published a study on the outcomes of 44,177 adults in South Africa, approximately 10% of all those starting public sector ART nationally between 2002 and 2007.[3] Based on routinely collected data, the study provides insight into the effectiveness of a large national ART program and has implications for other low-income and middle-income countries working toward universal ART access.

We found evidence of the rapid massive scale-up of ART: enrollment increased 12-fold over 5 years, and 63% of all patients were enrolled in 2006/2007. There were strong temporal trends in patient retention. Attrition was highest in the first year on ART but continued with duration on treatment: overall retention at 12, 24, and 36 months was 80%, 71%, and 64%, respectively. Over time, patient attrition was increasingly due to loss-to-follow-up (LTFU) compared with mortality, suggesting that there may be different risk factors for early and late attrition on ART. With each successive calendar year of enrolment, too, there was an increasing risk of appearing LTFU. For example, the risk of appearing LTFU at 12 months on ART was 12 times higher among patients enrolled in 2007 than those enrolled in 2002/2003 (adjusted hazard ratio: 11.9, 95% confidence interval: 6.4 to 22).

At a program level, it is important to characterize the patients defined as LTFU. Some will have been misclassified LTFU, either because they are dead[4] or because they have interrupted treatment temporarily[5]; some patients recorded as LTFU will have been lost to care, having stopped treatment altogether, whereas another group will be alive and in care but considered LTFU because of administrative error including unrecorded visits and transfers. True retention in care may thus be underestimated.

By the end of 2009, South Africa had initiated nearly 1 million individuals on ART.[2] The growing challenge for South Africa and other countries with large long-term ART programs is to find better ways of following and retaining as many of these patients as possible in life-long care.

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Retention on Antiretroviral Therapy in National Programs in Low-Income and Middle-Income Countries

To the Editors:

The study from Cornell et al on a sample of approximately 10% of patients started on antiretroviral therapy (ART) in the public sector in South Africa showed an increasing proportion of patients lost to follow-up (LFU) among patients starting in most recent years.[1] These results are of major public health importance considering the risk of HIV drug resistance.[2] We agree with the authors that monitoring the retention on ART is complex and interpreting data needs to consider potential bias in classifying patients LFU.

Each year, the World Heath Organization and partners are collecting national programs data including retention on ART.[3] In 2009, the number of

countries reporting and the number of patients assessed almost doubled compared with 2008.[3] Among sub-Saharan Africa countries, average retention at 12, 24, and 36 months was 74.5%, 71.9%, and 70.4%, respectively, which is within similar range of the 2008 results.[4] Because 2009 data included part of data reported in 2008, a trend analysis is not possible. We observed a large variation between countries; retention at 12 months ranged between 47% and 96%. Such differences cannot be attributed only to program performance, but also reflect the capacity of patient monitoring systems. First, retention is overestimated when calculated exclusively on survival without taking into account patients' LFU and those interrupting treatment. Second, improper recordkeeping of patients transferred from one health facility to another to continue treatment may result in misclassification as LFU, hence underestimating retention. This bias, discussed by Cornell et al, may increase with time as a result of more facilities offering ART resulting in more opportunities for patients to be transferred. In addition, country data may not be representative of the full program when produced from nonrandomly selected sites.

In 2009, a review of national monitoring systems conducted in 13 countries in southern and eastern Africa revealed significant variations among countries and health facilities to effectively monitor the outcomes of people on ART. All countries had multiple paper-based and electronic systems that were not interoperable. Data from facilities within the countries have different levels of quality, hence affecting their accuracy and representativeness at the national level. Only seven countries had data quality assessments conducted in the past 5 years (Dick Chamla, personal communication).

To document program performance, retention on ART should be produced for each cohort of patients starting in a specific year and also for longer follow-up to assess the long-term retention on ART; in 2009, at a global level, 81% of national ART programs were established for more than 5 years.[3] Although accurate data are as critical for patient management than for monitoring programs, open lifelong cohort monitoring for HIV care and ART presents with unprecedented challenges as a result of the growing number of patients and increasing follow-up. We share our colleagues' concern of achieving an accurate, simple, and sustainable monitoring system of patients in HIV care and ART, ascertaining outcomes in patients classified as LFU.[5]

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ERRATUM

Kaposi Sarcoma-Associated Herpesvirus Serum DNA and Antibodies Not Associated With Subsequent Non-Hodgkin Lymphoma Risk: Erratum

The article by Beachler et al, appearing in the *Journal of Acquired Immune Deficiency Syndromes*, Vol 56, No. 2, pp. 188–192 entitled "Kaposi Sarcoma-Associated Herpesvirus Serum DNA and Antibodies Not Associated With Subsequent Non-Hodgkin Lymphoma Risk," an author's name was printed incorrectly. "Charles C. Rabkin" should actually be listed as "Charles S. Rabkin."

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