High viral suppression and low attrition in healthy HIV-infected patients initiated on ART with CD4 above 500 cells/μL in a program setting in Uganda

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Abstract
Background: The World Health Organization recommends antiretroviral therapy (ART) for all HIV-infected patients at all CD4 counts. However, there are concerns that asymptomatic patients may have poorer viral suppression and high attrition.
Objectives: We sought to determine attrition and viral suppression among healthy HIV-infected patients initiated on ART in program settings.
Methods: This cross-sectional study enrolled ART-experienced patients attending two PEPFAR-supported, high-volume clinics in Kampala, Uganda. Eligible patients were >18 years and had completed at least six months on ART. Participants were interviewed on socio-demographics, ART history and plasma viral load (VL) determined using Abbott Real-time. Predictors of viral suppression (<75 copies/ml) were determined using multivariate logistic regression.
Results: Overall, 267 participants were screened, 228 were eligible and 203 (89%) retained in care (visit within 90 days). Of the 203 participants, 115 (56.7%) were key-populations. Viral suppression was achieved in 173 patients (85%; 95% CI, 80.3%-90.1%). The factors associated with viral suppression were prior VL tests (AOR 6.98; p-value <0.001) and receiving care from a general clinic (AOR 5.41; p=0.009).
Conclusion: Asymptomatic patients initiated on ART with high baseline CD4 counts, achieve high viral suppression with low risk of attrition. VL monitoring and clinic type are associated with viral suppression.
Keywords: Key populations, viral load, acquired immunodeficiency syndrome.
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Introduction
HIV/AIDS remains a major public health challenge globally. By the end of 2017, there were 36.7 million people living with HIV/AIDS (PLHIV) globally[1]. Over the last decade, the HIV response and efforts towards ART scale-up have been successful. As of 2018, it is estimated that 21.7 million people are receiving ART, 15.3 million

of whom were in sub-Saharan Africa1. The availability of less toxic, more efficacious and simpler ART regimens with less daily dosing frequency, together with increasing evidence that favors earlier ART initiation[2–5] have been the catalysts for the scale-up. To this end, the World Health Organization (WHO) revised HIV treatment guidelines in 2015 with recommendation for universal ART at all CD4 cell counts[4]. This recommendation has been endorsed by many countries, including the Uganda Ministry of Health (MoH). The new guidelines have dramatically increased the number of patients accessing ART at higher baseline CD4 cell counts. In 2018, the President's Emergency Plan for AIDS Relief (PEPFAR) and donor agencies unveiled "surge strategy" with an overall aim of closing the remaining gap in ART coverage[6]. Therefore, the number of healthy HIV-infected patients accessing ART is expected to rapidly and significantly increase. To mitigate the operational challenges associated with the rapid scale-up of ART, WHO and donor agencies have advised countries to decentralize HIV care through the implementation of differentiated service delivery models[7,8]. These models have been adopted by many countries in SSA.

In the year 2014, The Joint United Nations Programme on HIV/AIDS (UNAIDS) unveiled the "90-90-90" treatment goals with an ultimate aim of ending the HIV epidemic by the year 2020. The goals are meant to have at least 90% of PLHIV tested for HIV, at least 90% of the diagnosed patients initiated on ART and achieving at least 90% viral suppression rate in PLHIV receiving ART. Countries are expected to achieve the goals, including in key populations (sex workers, men who have sex with men). However, there are still treatment gaps in resource limited settings (RLS)[9], including Uganda[6] and, reaching the UNAIDS goals requires new innovations to enhance current ART delivery models and support health systems in the high-burden countries. Although clinical trials studies conducted in resource-limited setting have reported high viral suppression rates in patients initiated on ART with high baseline-CD4-cell counts[2,3,10], it is unclear whether healthy patients especially key populations (KPs) accessing ART within HIV programs in SSA countries will achieve the 90% viral suppression target. The key barriers to achieving high and durable viral suppression in asymptomatic patients include poor adherence and lack of motivation for ART[11–13]. These barriers to ART adherence are even more concerning for programs that target populations with behavioral barriers to ART adherence-for example, key populations (KPs), adolescents, men and young women. Key populations con-tribute a significant proportion of new HIV infections in SSA[14] yet studies continue to show that KPs, despite being targeted for early ART, may not achieve the 90% viral suppression target[15]. In addition, there are concerns that the rapid scale-up of ART may disrupt HIV care programs in resource-constrained countries, especially in SSA countries[16].

To understand the success of ART scale-up, we sought to determine attrition and viral suppression rates in a KP-predominant population accessing ART with baseline CD4 cell counts above 500 at prototypical high-volume, PEPFAR supported clinics in Uganda.

Methods

Study Setting

The study was conducted at two high-volume urban HIV-clinics; The Mulago Immunosuppression (ISS) and the Most-at-risk Populations Initiative (MarPI) clinics. The clinics mainly serve urban population around Kampala and receive funding from PEPFAR. The ISS clinic provides HIV care to a general population while the MARPI clinic exclusively serves Key populations (sex worker and men who have sex with men). Both clinics follow the WHO and MoH guidelines on antiretroviral therapy. The clinics have adopted the use of viral load tests to monitor ART success and provide a comprehensive HIV care package in line with the Uganda HIV treatment guidelines[17]. Prior to the 2015 WHO guidelines, patients routinely had CD4 monitoring tests every six months to determine ART eligibility.

Study population

From August 2015 through March 2016, HIV-infected receiving ART at the two study clinics that were consecutively assessed for eligibility for enrollment. Eligible patients were aged at least 18 years, were receiving the Ministry of Health recommended first-line ART regimen, had baseline CD4 higher than 500 and had completed at least six months on ART.

All participants had been initiated on ART between December 2013 and September 2015 and had therefore been on ART for at least six months. This period coincided with the period when WHO and the Ugandan Ministry of health recommended ART at all CD4 cell counts for KPs and priority group18 and raised the threshold for ART from CD4 cell count of 350 to 500 for the general population. At the time of the study, ART at all CD4 cell counts was only recommended for children aged less than five years, Hepatitis B co-infected patients, key-populations (sex workers, men who have sex with men) and priority populations (pregnant and lactating mothers, fisher folks, uniformed personnel, intravenous drug users, and truck drivers). Eligible patients were aged at least 18 years, were on the Uganda Ministry of Health recommended first line ART regimen, had baseline CD4 above 500 and had completed at least six months on ART.

Study procedures

We used the electronic medical records (UgandaEMR) at the two study clinics to identify potential participants for enrollment. Clinical records for identified individuals were reviewed to confirm eligibility and participants who met the study criteria and were active in care (clinic visit within 90 days) were then contacted at their nearest scheduled clinic appointment for interviewing and HIV RNA determination. Data on ART treatment history (ART regimen, duration, dosing and frequency; prior adherence record and ART interruptions) and laboratory results (prior viral load and CD4 tests) were obtained from patient charts, registers or UgandaEMR. Patient reported adherence was determined using the 3-day recall method. Adherence was deemed good if patients reported no missed pills within three days prior to study interviewing. Participants were then interviewed on their socio-demographics, medical history and a targeted symptom screen and physical exam done. Results of viral load (HIV RNA) test done within 3 months of study enrollment was deemed current. Patients with no current viral load results had phlebotomy and HIV RNA assay done using Abbott RealTime© at the Uganda National laboratory Services

Statistical analysis

We used STATA version 14.1 (STATA, College Station, TX) for study analyses. We determined proportion of patients lost-to-follow up (LTFU) as well as proportion of patients with undetectable and supressed HIV RNA (HIV RNA<75 copies/ml and HIV RNA<1000 copies/ml respectively). We used bivariate and multivariate logistic regressions to determine the factors associated with viral suppression (HIV RNA < 75copies/ml). Predictors with p-value <0.1 in the unadjusted analysis at the bivariate analysis stage were included in the multivariable analysis. Age, sex, and adherence were forced in the model because their importance in HIV programming and compelling association with viral suppression from literature.

Ethics

The School of Medicine Research Ethics Committee (SOMREC) of Makerere University, Kampala, Uganda approved the study (¬REC-REF 2015-083). All study participants provided written informed consent for study participation before enrollment. Participants with detectable viral loads had their treatments reviewed and appropriate actions taken.

Results

Study recruitment

From August 2015 through March 2016, 267 participants were consecutively assessed for eligibility. Of these, 288 were eligible for enrollment. Thirty-nine participants were excluded from the study due to missing data on study eligibility (n=20), duration of ART less than 6 months (n=8), receiving second-line ART (n=4), baseline CD4 cell count <500 after chart review (n=7) (Figure 1).

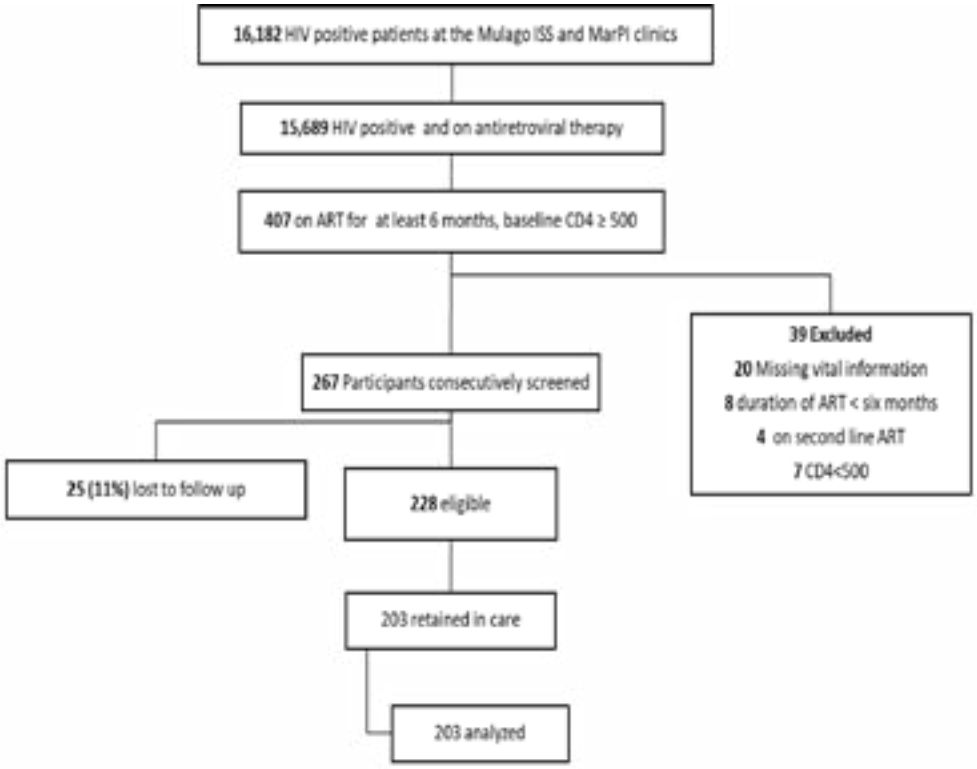

Figure 1: Enrollment of the 203 study participants
Patients were prospectively screened and eligible patients enrolled until sample size was accrued. *Note:* LTFU-lost to follow-up, MarPI-Most at risk population, ISS-Immunosuppression.

Of the 228 participants eligible for study recruitment, 25 (11%) patients were LTFU (no clinic visit in 90days) while 203(89%) were retained in care (made a clinical visit within 90 days of a scheduled visit) and were available for study interviewing and HIV RNA determination. Of the 203 participants, 115 (56.7%) were key populations (sex workers, men who have sex with men) and 126 (62%) had been on ART for at least one year. The median age and baseline CD4 cell counts were 30 (IQR; 25-35) years and 662 (IQR; 547-774) cells/μl respectively. Eighty-one percent (165/203) of the study participants were female and 64% not married. Ninety-four percent (190/203) of the study participants were taking once-a-day single pill that consisted of efavirenz (EFV) co-formulated with tenofovir disoproxil fumarate (TDF) and lamivudine (i.e., EFV/FTC/3TC); the MoH first line recommended first option of the MoH first line ART regimen then. At the time of ART initiation, 94.5% (n=203) of all study participants had WHO clinical stages one or two. The median age (IQR) and baseline CD4 (IQR) of the 25 patients excluded from analysis of viral suppression were 29.3 (24.8-35.2) years and 642 (510-996) cells//μl. Therefore, there was no difference between the excluded and analyzed patients with regard socio-demographics.

Viral suppression

Undetectable HIV RNA (<75copies/ml) was observed in 173 (85%; 95% CI 80.3% - 90.1%) participants. Using the viral suppression threshold recommended by WHO (HIV RNA <1000 copies/ml), 192/203 (94.6%; 95% CI 90.4% - 97.0%) participants had viral suppression. If all patients LTFU were assumed to be viremic, the viral suppression rate was 75.9% (173/228) and 84.2% (192/203) using the <75 and 1000 copies/ml cut-offs respectively. Viral suppression in the key-populations was observed in 107/115 (93%) participants (Figure 2). Of the 203 study participants who had viral load determined, 11(5.4%) patients had HIV-RNA >1000 copies/ml while 19 (9.4%) had low-level viraemia (75 copies/ml<HIV RNA<1000 copies/ml). Of the 11 patients with HIV RNA>1000 copies/ml, nine of whom were from MARPI clinic and eight were FSW. Three participants, one of whom was pregnant at the time of ART initiation had viral loads of more than 100,000 copies per ml.

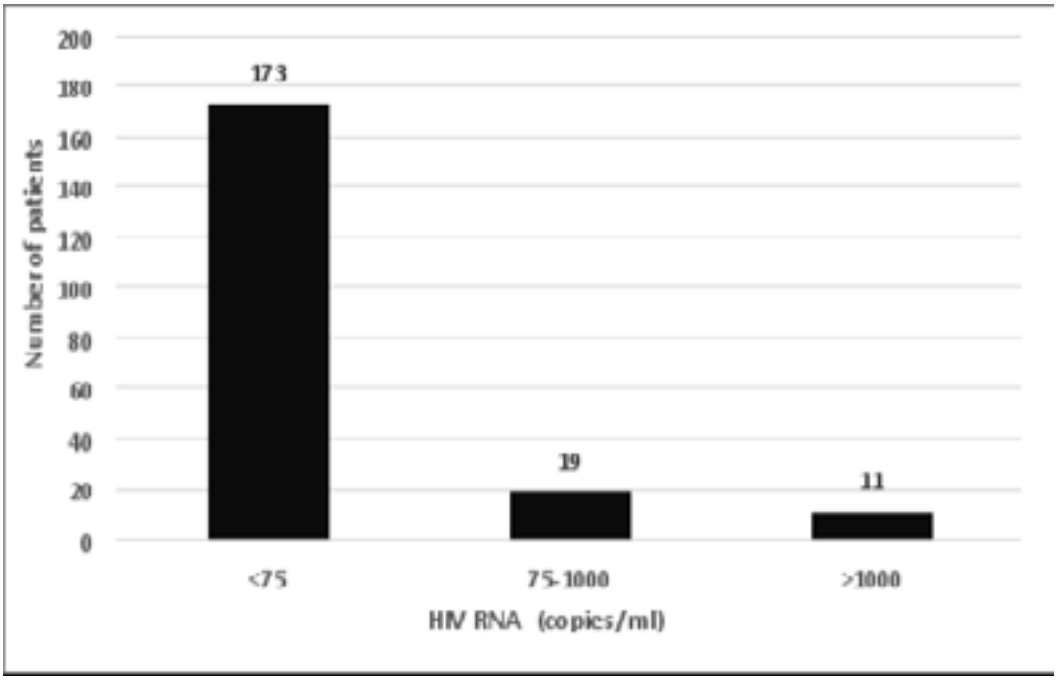

Figure 2: Distribution of viral load in the 203 enrolled study participants
Viral suppression (HIV RNA<75 copies/ml) was achieved in 173/203 patients.
19 patients had low-level viremia (75 copies/ml. *Note:* HIV means Human Immunodeficiency Virus

Adherence to antiretroviral therapy in the study participants

Of the 198 participants with record of adherence assessment, 175 (88%) reported good adherence (no missed ART within 3 days prior to study enrollment). Of the 23 participants who reported missing ART for at least one day, only three patients reported missing ART on all the three days. All the participants who missed ART for 3 days had missed appointment visits prior to the study interview.

Table 1: Demographic and clinical characteristics of the 203 enrolled study participants

Characteristic	*Number (n=203)*	*Percent*
Demographic characteristics		
Age (years)-Median (IQR)		31 (25-35)
Female	172	84.62
Marital status		
Married	68	33.50
Not married Separated	135	66.50
Highest education level		
None/Primary level	107	52.71
Secondary/Tertiary level	96	47.29
HIV clinic		
ISS	101	49.75
MARPI	102	50.25
Treatment history		
One pill /day ART formulation*	190	93.60
Duration on ART ≥1 year*	126	62.07
Clinical Characteristics		
Baseline HIV WHO stage**		
Stage 1or 2	188	94.5
Stage 3	11	5.5
Laboratory Characteristics-Median (IQR)		
Baseline CD4 (cells/µl)		662 (547-800)
Baseline WBC (cells/µl)		5360 (4460-11000)
Baseline HB (g/dl)		13.6 (12.5-14.5)
Reason for ART initiation		
FSW	106	52.2
MSM	8	4.4
Discordant couples	17	8.4
Pregnant/ Lactating	46	22.2
Others$^{\beta}$	26	12.8

Characteristics of the enrolled study participants. Overall, majority of the patients were female, not married, taking a single-pill ART and engaged in a sex work.

Note:

1. ISS denotes Immunosuppression; MARPI-Most-at-Risk Populations Initiative; FSW-Female sex workers; MSM-Men who have sex with men.
2. **4 missing HIV stage, *2 missing number of ART pills per day and ART duration.
3. $^{\beta}$Others included fisher folks (5), truck drivers (10), and uniformed officers (7) and bar maids (4)

Predictors of undetectable viral load (HIV RNA <75 copies/ml) in the enrolled participants

In a final logistic regression model adjusting for age, sex, adherence, clinic of care, prior viral load monitoring, education, WHO stage and reason for ART initiation, the factors associated with viral suppression included; a prior viral load monitoring test (adjusted odds ratio (AOR) 6.98; 95% CI 2.63-18.50; p-value <0.001) and receiving care from Mulago ISS clinic (AOR 5.41; 95%CI 2.63-18.50; p-value=0.009). There was no association between viral suppression and age, sex, the level of education. There was a trend towards an association between adherence and undetectable viral load but this did not meet the statistical significance threshold (AOR 1.71; 95% CI 0.44-6.58, p value 0.434) (Table 2).

Table 2: Factors associated with undetectable viral load in the 203 enrolled participants

Variable	OR (95% CI)	p-value	aOR (95% CI)	p-value
Sex				
Male	1		1	
Female	1.12 (0.31-4.02)	0.755	1.17(0.32-4.27)	0.809
Age				
>35	1		1	
25-35	1.01 (0.37-2.74)	0.986	2.10 (0.59-7.43)	0.251
<25	0.78 (0.23-2.67)	0.690	2.35 (0.49-11.20)	0.284
Clinic				
MARPI	1		1	
Mulago ISS	6.23 (2.3-17.0)	<0.001	5.41 (1.52-19.27)	**0.009***
Education				
Secondary/Tertiary	1		1	
None/Primary	1.95 (0.89-4.27)	0.094)	2.02 (0.79-5.31)	0.156
Adherence				
No missed pills	1		1	
Missed Pills	2.09 (0.52-8.30)	0.297	1.71(0.44-6.58)	0.434
Prior VL test				
No prior test	1		1	
Prior test	11.92 (5.0-28.7)	<0.001	6.98 (2.63-18.50)	**<0.001***
Reason for ART initiation				
Pregnant/ serodiscordant	1		1	
FSWs	1.51 (0.61-3.72)	0.375	1.26 (0.43-3.64)	0.671
Other KPs	0.65 (0.23-1.84)	0.415	1.04 (0.29-3.69)	0.956

Logistic regression for factors associated with viral suppression. *Note:* VL-Viral load, KPs-Key populations; ISS Mulago Immunosuppression Clinic; MARPI-Most at Risk Populations Initiative Clinic; FSW-Female sex workers; MSM-Men who have sex with men; AOR-adjusted Odds Ratio. Serodiscordant means patients involved in HIV serodiscordant relationship **p-value* <0.05

Discussion

In this cross-sectional study to determine attrition and viral suppression rates in healthy HIV-infected patients initiated on ART with high in program settings, there was low attrition and high viral suppression. The factors associated with un detectable viral load were prior viral load monitoring test (s) and receiving care from a general (non-key population) clinic. This study gives preliminary results on the outcomes of healthy patients initiated on ART with high CD4 cell counts in HIV programs in resource-constrained settings in the era of ART scale-up.

In this study, the viral suppression rate, as determined using the WHO viral suppression threshold (<1000 copies/ml), was higher than the UNAIDS 90% target and the national suppression rate (89%)[19]. However, using the lowest limit of HIV RNA detection (75 copies/ml), viral suppression rate was lower than the UNAIDS target. The viral suppression in this study is similar to rates in clinical trials involving healthy patients. In the "Early HIV Therapy in Patients With High CD4 Cell Counts (EARLI)"and the "Strategic Timing of Antiretroviral Treatment (START)" trials, viral suppression was achieved in 96% and 98% of study participants after six and twelve months of ART respectively[3,10]. The two studies enrolled patients with CD4 cell counts higher than 350 cells/μL and 500 cells/μL respectively. Results from other test and treat trials have reported that patients initiated on ART with CD4 cell counts higher than 500 are less likely to have detectable viral load at one year[20,21]. The viral suppression rate in our study is also comparable to results

from observational studies involving ART-experienced asymptomatic patients in programming settings[22]. Therefore, our results provide an assurance that healthy patients can achieve viral suppression higher than the UNAIDS 90% target.

Despite the high viral suppression rate, a significant proportion of participants (9.4%) had low-level viraemia (75<HIV RNA<1000 copies/ml). Studies involving patients with advanced HIV and low-level viremia have reported increased risk of viral rebound[23] and more rapid decline in CD4 cell counts[24] in patients with low-level viraemia. Therefore, patients with low-level viraemia require intensive adherence support.

Viral suppression in our study was much higher than results from earlier studies enrolling similar populations in program based care[25,26]. The high rate of viral suppression in this study and other recent studies may be due to the currently recommended simpler and more efficacious ART regimens.

With regard to the factors associated with viral suppression, prior viral load test(s) and receiving care form a non-key population clinic were associated with viral suppression. Although, viral the benefits of viral load monitoring in HIV care has been well described and is currently emphasized[18,27], there is limited data on whether viral load testing improves viral suppression. Similar to our study, a recent study in Uganda has highlighted the importance of viral load monitoring and counseling in improving viral suppression rates in a program setting[28].

In this study, age, sex, adherence, reasons for ART initiation and education level were not associated with viral suppression. This may be due to the similarity of barriers to optimal adherence across the different groups. Surprisingly there was no association between participant reported adherence and viral suppression in this study. The lack of a statistically significant relationship between adherence and viral suppression may be as a result of a small sample size, as evidenced by relatively wide confidence intervals.

Overall, attrition was low for a study population that predominantly enrolled key-populations in urban settings. The attrition rate in this study is similar to attrition rates reported in studies involving healthy asymptomatic patients[29] but lower than attrition rates in the general population. Patients with high CD4 are relatively healthy and asymptomatic, economically productive[30] and can afford the costs attending HIV clinics. However, data from option B-plus programs in SSA reported that pregnant women initiated on ART with higher baseline CD4 cell counts were more likely to be LTFU[31]. This observation suggests that mothers accessing ART while pregnant may require intensive psychosocial support.

Our study is not without weaknesses. The study design cannot support causal relationship between the studied factors and viral suppression. The study offers a one-time snapshot of viral suppression in a relatively young cohort. As a result, the durability of viral suppression remains to be determined. We did not ascertain HIV RNA in patients lost to follow up. Therefore, overall viral suppression is likely to be lower. However, even when an intention to treat analysis was done with assumption that all patients LTFU had viral load above the suppression threshold, viral suppression remains high.

Conclusion

In healthy HIV-infected patients accessing ART in program settings viral suppression surpassed the UNAIDS 90% viral suppression threshold with a low risk of attrition. Viral suppression was equally high in key-populations as well as the general population. Viral suppression was higher in patients with prior viral load tests as well as patients receiving care from a general HIV clinic. The findings demonstrate the importance of viral load monitoring in achieving viral suppression in HIV programs in resource-constrained settings. Despite the high viral suppression rate, there was a relatively high rate of low-level viremia. Therefore, strategies aimed at improving retention and promoting sexual behavior change are needed in HIV programs targeting KPs.

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Conflict of interest

None to declare.

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