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Extending Dispensing Intervals for Stable Patients on ART

To the Editors:

Over the past decade, antiretroviral therapy (ART) programs have been rapidly expanded in resource-limited settings. South Africa has the largest ART program in the world with nearly 2 million people accessing treatment.[1] ART Adherence Clubs (ACs) have been implemented in the Western Cape of South Africa to improve long-term retention in care for stable ART patients by providing quick and patient-friendly access to treatment and care while decreasing the burden on overstretched health care facilities.

ACs are facilitated by a lay club facilitator and consist of approximately 30 stable patients who meet every 2 months either at the health facility or in a community venue. Patients are eligible to join an AC if they have been on the same ART regimen for 12 months or more, have had 2 consecutive undetectable viral loads, and do not have any other medical condition requiring more frequent follow-up. Each visit consists of a quick clinical assessment and on-site dispensation of prepacked ART with a nurse available for referral as necessary.[2] Early evidence suggests ACs are effective in retaining stable patients in care with high levels of virologic suppression.[3]

These findings were presented at the International Conference on AIDS & STIs in Africa, December 2013, Cape Town, South Africa.
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Migration is common in sub-Saharan Africa where patients move away from home for economic reasons. This movement results in circular migration patterns that impact adherence and retention in antiretroviral care. In the Western Cape, many patients return to their province of origin over the holiday period of December/January and do not seek care while away. This migration puts patients at risk of ART interruptions and defaulting care, especially when time away from the Western Cape is extended beyond the period initially intended due to unforeseen circumstances.[4] The extent of this seasonal migration has not been quantified, but experience at the clinics suggests that most patients are affected.

Current ART pharmacy guidelines in South Africa require ART scripts to be written every 6 months despite national adult ART guidelines that only require an annual clinical assessment for stable ART patients. Although national policy allows 3-month dispensing, there is great variation between provinces and individual facilities. Accordingly, stable patients in the Western Cape receive a maximum of 2 months of ART per visit. To support ART patients who most commonly migrate over the holiday period, ACs that were scheduled to meet between mid-December 2012 and mid-January 2013 were given 4 months of ART in their October/November 2012 AC visit. Four months of ART were dispensed as two 2 monthly supplies to align with national policy. Data are limited on how long ART dispensing intervals should be to optimize retention in care. The objective was to compare outcomes among AC members who received 2-month ART (normal standard of care) to 4-month ART.

The Hannan Crusaid Treatment Center in Gugulethu and Ubuntu Site B Clinic in Khayelitsha are large treatment facilities in periurban, high-prevalence areas of Cape Town, South Africa. Both services have been described, in detail, previously and are or have previously been supported by the nongovernmental organizations Desmond Tutu HIV Foundation and Médecins Sans Frontières, South Africa, respectively.[5–11]

All adult ACs at the Hannan Crusaid Treatment Center and Ubuntu Site B Clinic who were enrolled in an AC before the end of 2012 were included in the analysis. Adult ACs include stable patients of 18 years or older. AC procedures at the 2 sites are similar.

Data presented includes the number and proportion of patients receiving each interval of ARVs overall and by site. ACs were assigned to receive either 4 or 2 months of treatment based on when their December/January visit was scheduled. ACs with a scheduled visit between 17 December and 18 January were assigned to the 4-month group. Outcomes of patients who received two 2-month prescriptions simultaneously (ie, 4 months) of ART (group A) are compared with those who received the standard 2 months of ART (group B). Outcomes include the proportion of patients defaulting from ACs 4 months after their final visit in 2012 and for those with blood results in 2013 the proportion of patients who were not virally suppressed (viral load above 400 copies/mL). Associations by group were assessed with χ^2 tests.

A total of 1860 patients in 1 of 76 ACs were eligible for the analysis (Table 1). Over the holiday period, 42 ACs were given 4 months of ART and 34 ACs were given 2 months of ART. Four months after the final AC visit in 2012, 4.0% had defaulted care overall [group A, 41 of 1054 (3.9%); group B, 33 of 806 (4.1%)]. There was no difference in the risk of defaulting from an AC in group A who received 4 months of ART compared with group B who received 2 months of ART (risk ratio, 0.95; 95% confidence interval: 0.61 to 1.49; $P = 0.82$). Of the 1507 of patients with a blood draw at their first or second 2013 visit, 3.6% were not virally suppressed [group A, 31 of 842 (3.7%); group B, 23 of 665 (3.5%)]. No significant associations were observed between viral suppression and group (risk ratio, 1.06; 95% confidence interval: 0.63 to 1.81; $P = 0.82$). Between the last visit of 2012 and the first schedule visit of 2013, none of the club patients died.

This analysis was limited to 2 sites where 4 months of ART was provided to those clubs whose 2-month return date would have fallen in December or the first part of January.

TABLE 1. Comparing Outcomes of Adherence Club Members Receiving 4 Months vs. 2 Months of ART

		Defaulting					
	No. ACs	Total	In Care	Defaulted	Defaulted, %	Risk Ratio (95% CI)	*P*
Overall							
Group A: 4 mo	42	1054	1013	41	3.89	0.95 (0.61–1.49)	0.823
Group B: 2 mo	34	806	773	33	4.09		
Total	76	1860	1786	74	3.98		
Site 1							
Group A: 4 mo	24	648	627	21	3.24	0.65 (0.37–1.14)	0.132
Group B: 2 mo	20	500	475	25	5.00		
Total	44	1148	1102	46	4.01		
Site 2							
Group A: 4 mo	18	406	386	20	4.93	1.88 (0.84–4.22)	0.116
Group B: 2 mo	14	306	298	8	2.61		
Total	32	712	684	28	3.93		

	Viral Load					
	Total	<400	>400	Not Supressed, %	Risk Ratio (95% CI)	*P*
Overall						
Group A: 4 mo	842	811	31	3.68	1.06 (0.63–1.81)	0.817
Group B: 2 mo	665	642	23	3.46		
Total	1507	1453	54	3.58		
Site 1						
Group A: 4 mo	456	443	13	2.85	1.31 (0.55–3.12)	0.544
Group B: 2 mo	367	359	8	2.18		
Total	823	802	21	2.55		
Site 2						
Group A: 4 mo	386	368	18	4.66	0.93 (0.47–1.81)	0.823
Group B: 2 mo	298	283	15	5.03		
Total	684	651	33	4.82		

We only compared the short-term outcomes of the 2 groups. There was some variability in the proportion of patients defaulting in the 2 arms between sites. The small sample size restricted our ability to determine if these differences were meaningful. Although both sites were using the standardized AC model, there is potential for some factors to differ at the site level. Clubs in the 2 arms may have been operational for different amounts of time. A limitation of our data is that we only looked at extending 1 refill interval; and therefore, further research is needed to ascertain the impact of regular longer supply intervals.

Short-term outcomes among all AC patients were good with no difference in defaulting or viral suppression between groups. Longer ART supply refill intervals over holiday periods can support the extensive circular migration among patient populations without having a negative impact on patient outcomes. These findings also suggest that less frequent visits for stable ART patients should be evaluated as regular practice to alleviate an unnecessary burden on patients and clinic resources.

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Assessing the Public Health Impact of HIV Interventions: The Critical Role of Demographics

To the Editors:

HIV continues to spread and take the lives of millions around the world. Advances in antiretroviral therapy (ART) have substantially extended survivorship without completely removing the risk of transmission. Some preventive interventions have demonstrated efficacy in clinical trials,[1,2] but their effectiveness remains to be confirmed at community levels where the optimized level of implementation may not be replicable.

In a recent analysis, Kato et al[3] estimated the potential impact of expanding ART and combination prevention in Vietnam. Other mathematical models have also been used to project the public health impact of HIV prevention into sexually active populations.[4–10] Presented results in these modeling studies necessarily depend on various assumptions regarding population demographics, sexual behavior, and HIV transmission. With focus on the impact of the interventions, the primary interest falls on the ability of the proposed preventive method to reduce transmission, its acceptability by the targeted groups, the willingness of potential users to follow prescribed regimen and the public health risks associated with the new product (such as the spread of drug resistance associated with antiretroviral products). However, insufficient evidence is presented to justify the way processes of: (1) population recruitment, including immigration and sexual maturation, and (2) population departures, including emigration, age- and gender-specific mortality, infection-induced fatalities, and sexual inactivity, are modeled. In this commentary, we discuss the merits of the demographic assumptions used in Kato et al,[3] among other commonly used, and outline the need for their systematic reassessment.

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RECRUITMENT ASSUMPTIONS

Most of the published models on intervention impact assume that the number of individuals joining the population per year is constant (constant recruitment)[3,6–8,10–12] or proportional to the total population size (proportional recruitment).[4,5,9,13,14] In sexually active population with no immigration, constant recruitment implies that the same number of people reach sexual maturity annually. That may be an acceptable approximation over short periods of time, but becomes troublesome when the simulation period increases. The progression of HIV infection from acquisition to full-blown AIDS and death is incredibly slow and delayed even further by ART. Therefore, a meaningful impact of prevention intervention should be expected over several decades, which may explain why simulation periods of 20–50 years are used in mathematical models. Projections, presented in Kato et al,[3] are more than 40 years. If the population growth rate is 1% as currently estimated for Vietnam,[15] the cumulative growth over 40 years will be 49%. In comparison, the population in sub-Saharan Africa, which is impacted the most by the HIV epidemic, is growing at a rate of 2.2% per year[16] and is expected to be more than double by 2050.[17] It is not realistic to expect that the number of 15 year olds in these populations will remain the same over several decades. Proportional recruitment seems to address this issue but has the deficiency of connecting the current population size directly to the number of new recruits, that is, any change in the population size affects the cohort that joins the community instantaneously. However, the cohort of 15 year olds is more likely to depend on the population size when they were conceived, that is, 16 years before their sexual maturation. A delayed proportional mechanism, which is certainly more appropriate when sexually active populations are simulated, adds computational complexity and limits the analytical tools available to study the model behavior (comparison between some recruitment mechanisms is shown in Fig. 1A).

Another popular modeling decision is to assume that the cohort joining the population consists entirely of susceptible individuals.[3–12,14] In sexually active populations, the newcomers may be adolescents reaching sexual maturity or adults migrating into the community. We may agree that the prevalence of HIV among sexually inactive teenagers could be negligible because of the success of worldwide prevention strategies in mother-to-child transmission. However, that may not be the case for the migrating individuals. This is particularly important when analyzing populations with steady influx of people, such as the men-who-have-sex-with-men community in San Francisco or large metropolitan areas in Sub-Saharan Africa. Recent data from King County, Washington (including Seattle area), show that over a period of 5 years, 3 times more HIV-positive individuals have moved in than left the county. Ignoring the immigration of infected individuals, one may draw an imprecise picture of the drivers of the HIV epidemic or overestimate the projected impact of prevention interventions which target uninfected young adults by agglomerating all newcomers into that group (Fig. 1B).

DEPARTURE ASSUMPTIONS

Population departures are most often modeled assuming proportional rates of population losses per year because of sexual inactivity, HIV-related or HIV-unrelated causes, etc.[3–10] Problems with such assumptions arise in populations with strong gender imbalance in HIV-unrelated

