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Adherence to Anti Retroviral Therapy (ART) During Muslim Ramadan Fasting

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Abstract

Annual fasting during the month of Ramadan is observed in Muslim countries, some of which have widespread HIV infection. We studied treatment adherence and customary practices among 142 fasting 'FT' and 101 non-fasting 'NFT' patients on anti-retroviral therapy (ART) in Nigeria. Adherence on ART among FT and NFT patients was similar during Ramadan, 96% and 98%, and ever since commencement of ART, 80% and 88%, respectively. FT patients altered their typical daily behaviors by advancing morning and delaying evening doses thereby prolonging dosing intervals, eating heavier meals pre-dawn and on breakfast at sunset (78%), and changing or reducing their sleeping and waking times (40%). This preliminary study suggests that adherence and drug taking frequency appear uncompromised in FT HIV infected patients on ARVs.

Keywords

Adherence; Antiretroviral therapy; Fasting; HIV; Islam

Introduction

Annual Ramadan fasting (FT) is a fundamental religious rite in Islam observed by adult Muslims in many sub-Saharan African countries, such as Ethiopia, Kenya, Nigeria, Somalia, South-Africa, Tanzania and Uganda. These countries, have substantial Muslim populations, and also have considerable burden of Human Immunodeficiency Virus (HIV) infection. In fact, six of these 7 countries accounted for 51% of all cases in sub-Saharan Africa at the end of 2004 (UNAIDS 2005).

National Governments and multi-lateral organizations such as the World Health Organization (WHO), the Global AIDS Programs, United States' President's Emergency Plan For AIDS Relief (PEPFAR) and other Non-Governmental Organizations (NGO's) provide technical assistance, care and treatment, and have recently supported massive and rapid Anti-Retroviral Therapy (ART) expansion (Piot and Coll Seck 2001; Kamwi et al. 2006). However, in order to succeed, provision and expansion of ART should adapt to local and religious cultural

practices like Ramadan fasting and maintain fundamental principles of ART such as adherence. Sustained effectiveness of ART depends on long term, regular, fixed interval and time specific dosing schedules. Indeed sub-optimal adherence to ART not only reduces effectiveness, but is likely to lead to emergence of resistance and treatment failure in patients, and transmission of drug resistant virus strains within the community (Gallant 2002; Stevens et al. 2004). Another challenge is that concentrations of anti-retroviral (ARV) drugs must be consistently high (95%) and this is affected by local eating habits, foods and the timing of dosing schedules (Gallant 2002; Stevens et al. 2004).

The month of Ramadan can occur in any season, and the hours spent fasting 'FT' vary according to daytime duration, region (latitude) and season and usually lasts between 11 and 18 h. In Nigeria, Muslims strictly defer eating and drinking from dawn (0500 h) until dusk (1900 h), a FT period spanning 14 h daily for 29 or 30 days. A typical FT day follows eating high calorie, fatty and carbohydrate staples such as rice/yams, as well as fruits and water at 4:15 to 4:45 am. Actual FT commences before dawn at around 5:00 am and continues until sunset when breakfast is taken around 7:00 pm as recommended in the Qur'an, the Muslim holy book. Breakfast usually begins with a ritual eating of a few dates which is then followed by a meal of light to moderate quantity which may variously consist of fried chips/eggs, salad, tea, corn porridge and bean cake, meat/fish pepper soup and water. A second meal is eaten between 9:00 and 10:00 pm and is usually heavier comprising of foods such as pounded yam, glutinous rice or corn with chicken, beef or lamb soup. Muslims are strongly encouraged to spend more time in daily spiritual contemplation, prayers and Qur'anic recitation during Ramadan. Eating and sleeping patterns are usually altered to allow for these activities during the period.

Islam permits sick patients not to fast and to take medications during the month but many with chronic stable disease often insist on FT. Intake of drug doses is therefore difficult, and its adjustment to Ramadan is often not easy and adherence may be compromised. Here, we undertook preliminary evaluation of adherence to ARVs during Muslim Ramadan FT.

Methods

The study was conducted in Kano, a city with a predominantly Muslim population in northern Nigeria. At a PEPFAR supported facility, Aminu Kano Teaching Hospital (AKTH), Kano, Nigeria with approximately 2,500 initiated or maintained on ART since March 2005, adult patients maintained on ART who consented to participation were studied during the Ramadan lunar month (23 Sept–22 Oct 2006). Their demographics (age, gender, marital status and religion) and baseline clinical characteristics were recorded. Self reported adherence and customary practices were studied among fasting 'FT' and non fasting 'NFT' patients. Adherence was evaluated once by retrospective recall which was defined as the proportion of all doses actually taken, ever since ART commencement and during the month of Ramadan. Patients' case files (for retrospective data) and interviews with structured questionnaire administered during Ramadan were used to collect data.

CD4 cell counts and weights were repeated during Ramadan and changes from routine clinic values obtained pre-Ramadan (as documented in case files) were compared between the groups. Student's *t*-test, Wilcoxon rank-sum (*z*), Fisher's exact and Chi square (χ^2) tests and measures of effect were used for comparison between groups as appropriate, with $P < 0.05$ regarded as significant.

Results

A total of 243 follow up patients maintained on ART were seen during the Ramadan period with 142 FT and 101 NFT (Table 1).

The two patient groups were on similar three drug ARV regimens. The patients were on two drug back bone regimens of Zidovudine/Lamivudine (49.4%), Stavudine/Lamivudine (39.4%) or Tenofovir/Lamivudine (11.2%) coupled with a non nucleoside reverse transcriptase inhibitor (NNRTI), either Nevirapine (87.6%) or Efavirenz (10.0%), or a ritonavir boosted Protease Inhibitor (2.5%). The daily dosing frequencies were similar between FT and NFT patients with majority on twice daily regimens 132/142 (93.6%) and 94/101 (93.1%) ($\chi^2 = 0$, n.s.). For the Tenofovir/Lamivudine/Efavirenz regimen only one of 7 patients was on a once daily dosing, the ideal dosing frequency. The other six were dosed twice daily (3 patients) or thrice daily (3 patients).

The FT patients altered their typical daily behaviors during the Ramadan period by advancing their morning and delaying their evening doses giving a median dosing interval of 16.75 h (range 14.58–22.00 h), eating heavier, fatty meals at breakfast (78.2%), and altering and reducing their sleep time (40.1%).

Compared to pre-Ramadan values the median changes [and inter quartile ranges] in CD4 cell counts per ml in FT and NFT patients were similar +173 [75 – 312] and +143.5 [40 – 222] respectively (Wilcoxon ranksum, $z = 1.816$; $P > 0.05$). Similarly, the median changes in weight were -1.0 kg [-3.0 to $+0.5$ kg] and 0.0 kg [-3.0 to $+1.0$ kg] (Wilcoxon ranksum, $z = 0.901$; $P > 0.05$) respectively.

The proportion who never missed a dose among FT and NFT patients since ART commencement was 114/142 (80.3%) and 89/101 (88.1%) respectively with [Odds Ratio = 0.55 (95% CI 0.24–1.19)]. Those who did not miss a dose during the month were 136/142 (95.8%) and 99/101 (98.0%) respectively, with odds ratio of 0.46 (0.06–2.58). Six FT patients missed a dose during the month and suggested it could be related to FT.

The proportion who never missed a dose among NFT Muslim and Christian patients was 12/16 (75.0%) and 77/85 (90.6%) with odds ratio of 0.31 (0.07–1.66).

The proportion who felt or perceived having good to excellent health among FT and NFT patients was 139/142 (97.9%) and 92/100 (92.0%) with odds ratio 4.03 (0.93–24.04; Fisher's exact, $P > 0.05$) and new onset side effects were similar.

Discussion

This preliminary study suggests that adherence and drug taking frequency appear uncompromised in FT HIV infected patients on ARVs. FT had no untoward effects on body weight and CD4 cell count changes, health perception and tolerability but it led to changes in eating times, meal contents, sleeping pattern and dosing intervals. These behavioral changes appear mild but could alter the pharmacokinetics and pharmacodynamics of drugs, especially those with narrow therapeutic index, and consequently their effectiveness and tolerability. This potentially might lead to virologic failure and drug resistance. In chronic diseases like asthma, diabetes mellitus and epilepsy poor adherence to prescribed drugs during Ramadan may lead to therapeutic failures (Aadil et al. 2004; Benaji et al. 2006). In HIV infection, ARV regimens are designed so that the trough concentrations of the drugs are sufficient to suppress appreciable viral replication. The longer a dose is delayed however, the lower the concentration falls and the more viral replication occurs (Burger et al. 1998). Thus, it is possible therapy with ARVs having short half lives requiring ≥ 2 daily dosing may lead to sub-therapeutic levels during the FT period. These include Zalcitabine, Delavirdine and some un-boosted protease inhibitors (PI) like Indinavir, Nelfinavir and soft-gel Saquinavir. It has been shown that delaying an Indinavir dose leads to lower plasma concentration levels with subsequent viral replication and treatment failure (Burger et al. 1998). Of these ARVs only Nelfinavir is currently prescribed. Nelfinavir may be taken with meals twice instead of thrice daily at a higher dose, which should

be so recommended for FT patients. Other PIs which may be used include Lopinavir/ritonavir twice daily or Atazanavir once daily. Once-daily dose regimens (such as Tenofovir/Lamivudine or Emtricitabine/Efavirenz) should be advised for FT patients.

Secondly, eating behaviors changed, with 78% of FT patients ingesting heavy fatty meals pre-dawn and after sunset. Food ingestion is known to improve absorption or tolerance to certain ARVs. Therefore Ramadan FT makes it difficult to administer drugs that should be taken with food particularly for drugs dosed at least twice daily, i.e. Lopinavir/ritonavir and Nelfinavir. Conversely, food considerably reduces the absorption of didanosine and un-boosted Indinavir, and fatty meals may reduce the absorption and bioavailability of un-boosted Amprenavir and possibly Zidovudine. These should be considered when prescribing for FT patients.

Thirdly, changes in sleep, waking and eating times during the month noted in 40% of FT patients may alter the regularity of dosing time and circadian rhythm. There is conflicting evidence that such alterations in dosing time, circadian rhythm and diurnal variations may potentially affect the kinetics of ARVs, particularly protease inhibitors. For instance, in NFT state a reduction of one-third in area under the plasma concentration *versus* time curve (AUC) was observed after ingestion of the evening dose of ritonavir compared to the morning dose. However, no circadian variations were noted with Lopinavir/ritonavir combination (Hsu et al. 1997; Justesen and Pedersen 2002; van Heeswijk et al. 2005). Thus, the influence of changes in sleep, waking and circadian variations on ARV pharmacokinetics remains unclear.

Under these circumstances blood levels of ARVs may become unpredictable, inadequate or unsatisfactory for complete viral suppression. A rational approach to delivering ART is therefore desirable during FT. Firstly, certain ARVs are affected by heavy fatty meals and patients should be appropriately counseled. Secondly, ARVs with short half-life may drop to sub-therapeutic serum levels during fasting. In those on NNRTI containing 3 drug regimen, such a window may lead to patients remaining effectively on mono- or dual-ARV therapy in the latter half of the day as the NNRTIs have the longest half-lives. This has serious implications for emergence of resistance strains and eventually clinical failure. Cognizant of these facts, certain measures are recommended in initiating or maintaining ART during Ramadan fasting:

1. Use ARV combinations that can be taken once daily (e.g. Tenofovir/Lamivudine/Efavirenz).
2. Wherever possible use [ritonavir boosted] protease inhibitors (PI) that will reduce dosing frequency to once daily (e.g. Atazanavir) or twice daily ([e.g. Lopinavir/ritonavir], Nelfinavir).
3. Avoid use of ARVs with unfavorable pharmacokinetics (e.g. use of didanosine with food before or immediately after breaking fast).
4. Pre-Ramadan refresher training of adherence counselors and health care workers on best counseling practices for FT patients.
5. ARVs can be taken at 5 am and 7 pm. However, those specific times should be adhered to strictly and consistently during that period.
6. After Ramadan, one must return to 12-hourly schedule, strictly and consistently for twice daily dosed medications.
7. To select the new time from the FT timeframe (4–6 am or 6–8 pm), select one time [say, 7 am] and then add 12 h from that time [7 pm]. The new time would then be 7 am and 7 pm.

In those with HIV, prayer was mentioned as a very important factor in decision making about ART (Crane et al. 2000). It is likely spiritual activities like contemplation, FT and prayers might have positively influenced adherence to ART and perception of illnesses. Indeed feeling and perception of good health appeared marginally better among FT patients. Ways of improving adherence to ART and care through faith and religious based practices should be explored (Crane et al. 2000).

Nigeria has mixed Christian and Muslim populations and is one of the few places where the study could have been conducted. Expectedly, religion was significantly different between the groups though adherence was similar. But FT patients should be intensively counseled on

adherence as those who missed doses suggested there could be a relationship. Also, adherence was similar between NFT Muslims and Christians although other potential confounders like education and socio-economic status were not explored. Despite these limitations, the findings might potentially apply to other Muslim countries in and outside Africa as well as other FT practices (like the Christian Lent). But further local studies should be conducted given local variations in FT practices.

In view of the uncertainties highlighted above (circadian rhythm, feeding and short half-life) and with rapid ART expansion in Muslim countries, viral load and therapeutic drug monitoring that are more sensitive than CD4 cell changes and provide real-time outcomes should be employed in similar studies in the future.

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Table 1

Characteristics of fasting 'FT' and non fasting 'NFT' patients

Characteristic	Fasting (<i>n</i> = 142)	Nonfasting (<i>n</i> = 101)	Test statistic *
Age (years)	35.5 ± 8.3	37.5 ± 8.8	<i>t</i> = -1.859
Gender (Male/Female)	61/81	56/45	$\chi^2 = 3.687$
Marital status (Married, <i>n</i> %)	81 (57.0%)	66 (65.4%)	$\chi^2 = 1.70$
<i>Religion</i>			
Muslims	142 (100%)	16 (15.8%)	Fisher's
Christians	0 (0%)	85 (84.2%)	Exact ***
Pre-Ramadan weight (kg)	60.4 ± 13.1	63.8 ± 13.5	<i>t</i> = -1.015
Mean Karnofsky performance status, %	75.1 ± 12.6	72.4 ± 15.8	<i>t</i> = +1.517
Pre-Ramadan (On-ART) mean CD4 cell counts/ml	327.0 ± 199.7	301 ± 251.9	<i>t</i> = +0.894
Mean time on ART (months)	16.4 ± 15.3	13.0 ± 13.9	<i>t</i> = +1.596

* All test statistics were not significant, *P* value > 0.05

*** Significant, *P* value < 0.01