Chapter

Ageing and HIV-Risk in Non-Gravid Female Humans

Kelvin Leshabari, Godfrey Chale and Rashid Salim

Abstract

Objective: To estimate the association between ageing process markers (e.g. clinical conditions necessitating total abdominal hysterectomy) and immune functions (i.e. HIV-risk) among adult non-gravid female humans. **Materials & Methods:** We did a secondary data analysis, from a prospective, observational, hospital-based study conducted in Dar es Salaam, Tanzania. The primary study population included all women planned for Total Abdominal Hysterectomy (TAH). Target population was all women who underwent TAH. Data were analysed using a generalized linear model via SAS statistical software version 9.4. **Results:** We analysed 40981 women-hours of follow-up. None of the participant seroconverted against HIV during follow-up period, making an HIV-incidence of 0/40981 women-hours. All participants were black Africans (median age 42 (IQR: 37–47) years). We found a statistically significant drop (aOR: 0.687) in HIV-risk after age of 45 years. Serial correlation between age and HIV-serostatus was found (γ = -0.514, P = 0.000). Association between HIV and marital stata was barely significant (χ^2 = 8.0176, df = 3). **Conclusion:** There was a statistically significant reduced HIV-risk after the age of 45 years among hysterectomised women up and above the known behavioural/clinical risks. Participants who reported married had the highest HIV-seropositivity rate. **Recommendations:** These findings reflect antagonistic pleiotropy theory of ageing. Analyses on potential biological mechanism(s) against HIV in peri/post-menopausal women is/are warranted.

Keywords: ageing, antagonistic pleiotropy, endocrinology, hysterectomy, prospective, Dar es Salaam

1. Introduction

There is no doubt that human reproductive endocrine hormones display a handful of mysterious patterns in their ageing process. The patterns are debatable even among endocrinologists and physiologists alike. We did a secondary analysis of findings, to quantify part of the mysterious association, *of ageing process (surgical removal of endocrine uteri) and immune functions (HIV-risk) in non-gravid adult female humans*. Categorically, we asked ourselves whether there is any significant relationship between female reproductive endocrinology and HIV-pathobiology given the ageing process. We believe there is an unaccounted function(s) of reproductive hormones and HIV-pathogenesis in humans. Besides, the unknown function(s) seem(s) to function in a manner that is at present mysterious given the

current scientific knowledge base. We also considered the mystery to be descriptive to a number of other ageing related pathologies. The systemic reproductive endocrine mysteries reflect both structure and functions. At functional level, there exist frequent speculations, about mysterious benefits of endogenous progesterone (and even oestradiol?), against bacterial and viral invasions, along the reproductive tissues and cells. Otherwise, it is common knowledge in mammalian female embryology and anatomy, that during embryo-fetal development, premordial germ cells migrate, from the yolk sac to the gonadal ridge, and statistically populate the gonads. The movement is characterised by changes of the premordial germ cells into oogonia, in an unknown mechanism to science, even to the present day. Oogonia rearrange themselves into germ cell nests. These germ cell nests undergo a series of mitotic divisions. Oogonia enters 1st meiotic division as primary oocytes with arrest at diplotene stage until puberty. What exactly triggers those structural processes is still a mystery among scholars to date. The magic behind female mammalian reproductive endocrinology is not confined to structure.

There is palpable evidence to suggest that mammalian endocrine reproductive system is associated with a number of immune functions, some potentially beneficial against viral illnesses [1–4]. However, the concept of endocrine reproductive (dys)-functions against HIV infection in humans is only poorly understood [5]. For instance, Polis and colleagues have reported up to a 40% increased risk of HIV acquisition [6], associated with usage of progestin-based injectable contraceptives in adult females, specifically Depot Medroxy Progesterone Acetate (DMPA) [6]. However, much as the effects of potential confounding could not be completely ruled out in their study findings, it was still an interesting observation to our research group. Specifically, it followed logic, to check whether the same observation, was applicable to endogenous produced progesterone, in non-gravid state. Besides, most physiological functions of endocrine activities, and their effects on immune system, have been studied in adult males. Thus, the gap about the situation in adult females is widening, especially in the era of viral pandemics like SARS COV-2 and HIV/AIDS. It was on this basis, we hypothesised that *the female uterus, and its associated secretory functions, to be an important milieu, for enhancing HIV acquisition in humans*.

A number of actions displayed by female human reproductive system are associated with ageing process. For instance, it is still debatable among endocrinologists, on *how does the menstrual cycle coordinate itself*, *and cease to function after calendar time*, using hypothalamic-pituitary-gonadal axis. Besides, the uterine endometrium coordinates a handful of both reproductive and immunologic functions. Of importance to this chapter, uterine macrophages and epithelial cells have been shown to be key allies in mobilisation of innate defenses over calendar age [7, 8]. However, the exact cause behind the observation remains a matter of intellectual guess work among scientists to date. We hypothesized the observation to be related to probable endogenous progesterone and/or oestradiol effects.

Information on the relationship between gestation process in humans and HIV-infection is evident in published literature [9–14], and new information still accumulates rapidly [15–18]. Previous studies pinpointed potential biological mechanisms between endocrinology (i.e. endogenous oestradiol and progesterone effects) and immunobiology of HIV [4, 5]. However, most of this accumulated information tends to be biased due to samples used; characterised to be in gestational period, and therefore in an *altered physiologic state*. Little (if any) is known, about the contribution of endocrine functions, towards HIV-risk and HIV-disease process in normal

physiological states. To avoid biases associated with '*altered physiological processes*' prominent in gestational era, usage of non-gravid female humans, preferably after reproductive era, becomes justified.

There exists evidence about sex differences in immune responses among adult humans [1], but it is still not clear, the extent contributed by sex hormones, especially among adult female humans, in non-gravid state. We believe that, *there exists differential deleterious effects of female endogenous sex hormones, on HIV risks in non-gravid adult female human population*. However, to the best of our knowledge, the findings of this concept has not been evident in published literature to date.

Hysterectomy can simply be defined as *a surgical removal of the female uterus*. It can also include removal of adjacent structures (e.g. cervix) as evident in *total abdominal hysterectomy* and/or fallopian tubes and ovaries (*hysterectomy with (uni)-bilateral salpingo-oophorectomy*). Hysterectomy is the commonest gynaecologic surgery reported globally [19, 20]. We considered it as a natural surrogate equivalent of non-gravid state in our study cohort. Specifically, it offers a convenient platform, for analysing clinical and biological parameters associated with surgery, exclusively in non-gravid state. Effects of HIV on surgical indications and outcomes among women have been almost exclusively confined to Caesarean section. Caesarean section is an obstetric surgical procedure. Normal physiology in women, and their alterations in early stages of pathologic processes, can be best studied in non-gravid state. Thus, the quest for the interplay between female endocrine reproductive hormones (e.g. oestradiol and progesterone) and HIV pathobiology in non-gravid state remains unknown to the world of science. It was on this basis, we considered hysterectomised women as a natural reservoir to test our beliefs using a clinical research design and adopting specified statistical techniques in our hypothesis testing.

2. Methods

We did a secondary data analysis from a prospective, facility-based follow-up study, at all public regional referral hospitals in Dar-es- Salaam, Tanzania. Specifically, the study took place at Amana, Mwananyamala and Temeke regional referral hospitals. It was conceived as a clinical research study that assessed indications and outcomes of TAH in Dar es Salaam city, Tanzania. Dar-es-Salaam is a cosmopolitan city situated on the East-African coast. It is the business capital of Tanzania. The same city is projected to be 10th largest city on earth in population size come 2050. Geo-strategically, Dar-es-Salaam is a port city, and home to dozens of African demographic subsets, ranging from mainly the Bantu population group to African-Arabic mixed race population.

Data in the primary study was collected using a pre-designed clinical sheet that contained social, demographic, biological and clinical parameters on pre- and peri-480-hours post-hysterectomy. Specifically, HIV screening was accomplished using a serial algorithm involving SD Bioline HIV kit (SD Bioline HIV 1/2 3.0, Standard Diagnostics, Korea) to all participants. Those who were reactive on SD Bioline HIV test, confirmatory diagnosis was made using Unigold HIV kit (UniGold™HIV, Trinity Biotech Manufacturing Ltd, Bray-Ireland). Each participant was screened twice, first at the time of recruitment into the study, and again either before discharge from the ward post-operatively or anytime within 480-hours post-hysterectomy. Data collection started immediately upon a verbal informed consent for inclusion into the

primary study. Sample size was obtained using the prospective cohort formula from Kasiulevicius and others publication in the journal Gerontology back in 2006 [21];

$$\text{Sample size} = \frac{\left[\begin{array}{l} Z_\alpha\sqrt{\left(1+\frac{1}{m}\right)p^*(1-p^*)} + Z_\beta\sqrt{p1} \\ (1-p1)/m + p2(1-p2) \end{array}\right]^2}{(p_1-p_2)^2}$$

Z_α = Standard normal variate for level of significance.
m = Number of control subject per experimental subject.
Z_β = Standard normal variate for power or type 2 error as explained in earlier section.
$p1$ = Probability of events in control group.
$p2$ = Probability of events in experimental group p

$$P^* = \frac{p2 + mp1}{m+1}$$

For values of Z = 1.96, α = 0.05, β = 0.8, m = 1.

Study population in the primary study included all women with a surrogate marker for *ageing process* (clinical indications necessitating total abdominal hysterectomy). Target population referred to all women who underwent *total abdominal hysterectomy* at any of Dar es Salaam Public Regional Referral Hospitals. Thus, for a participant to be eligible for recruitment into the study, she had to be planned for *total abdominal hysterectomy* and/or emergency total abdominal hysterectomy due to a decision made on the operation table (in-theatre major adverse events) out of another planned surgery at any of those facilities during the study time. All women who underwent sub-total hysterectomies were thus excluded. The decision to do so originated from the assumption that, *for a woman to be planned for total abdominal hysterectomy, the clinical decision rule must incorporate a pathology associated with what we characterized as an ageing process*. Participants were recruited upon official notification for total abdominal hysterectomy at clinics (outpatients) or wards (inpatients) after clinical indications. Participants were followed-up to at most 480-hours post-operatively, or upon discharge from the ward post-operatively, whichever came first. Follow-up data included post-operative HIV serostata.

Data analysis was done using SAS software version 9.4 (SAS Institute, Cary-NC, USA). A minimum number of 106 women had at least 80% power of detecting a statistically significant difference at apriori 5% α-level. Continuous variables were summarised using median (with inter-quartile range). Categorical variables were summarized as proportion (with %). A generalised linear model was used to analyse data after appropriate validation of model assumptions. We considered at least 110 women as a rough estimate of effective sample size in cases of any potential refusal to participate/missing data. However, efforts were made to ensure minimal refusals to participate/missing information per participant via adoption of all surgical and nursing team members in the respective departments throughout the study period.

Ethical clearance for the primary study was obtained from ethical clearance committee at International Medical and Technological University (IMTU). Permission at referral facilities was sought from offices of municipal medical officers of health and facility in-charges of each hospital. Participants were approached with a verbal informed consent prior to recruitment into the primary study.

3. Results

We successfully analysed 40981 women-hours of follow-up. They consisted of all patients who underwent Total Abdominal Hysterectomy at Amana, Mwananyamala and Temeke regional referral hospitals from March to October 2017. In essence, none of the patient seroconverted against HIV during follow-up period, making an HIV-incidence of 0/40981 patient-hours. Their pre-operative HIV-serostata included 19 (17.76%) who were *reactive* on both screening tests, thereby considered as seropositive for HIV anti-IgG; 84 (78.5%) *non-reactive* on both screening tests and considered seronegative for HIV anti-IgG. Moreover, 3 (2.8%) patients refused screening. Therefore, their HIV-serostata remained unknown to study investigators. Likewise, 1 (0.93%) patient had discordant results between the two screening tests. All efforts to determine her HIV-serostatus during the time of hospital stay were deemed unsuccessful. All studied patients were black Africans by origin. The median age was 42 (IQR: 37.5–47) years. Serial correlation between HIV-serostata and age of patients yielded statistically significant findings ($\gamma = -0.514$, $P < 0.001$). **Figure 1** below highlights the pattern of the observed serial correlation between chronological age and HIV-serostata of participants.

To test for potential confounding, other variables (i.e. +/− of comorbidities, reported recent (past 1-month) sexual (oral, vaginal/anal) history, 1-month prior blood -(products) transfusion episode and place of residence) were also tested but yielded non-significant statistical evidence of confounding (χ^2-Yates corrected = 0.3833, df = 3). Converesely, it is worth noting that we also found a just significant correlation between reported marital and HIV stata (see **Tables 1** and **2** below) on univariate analysis during initial data exploration.

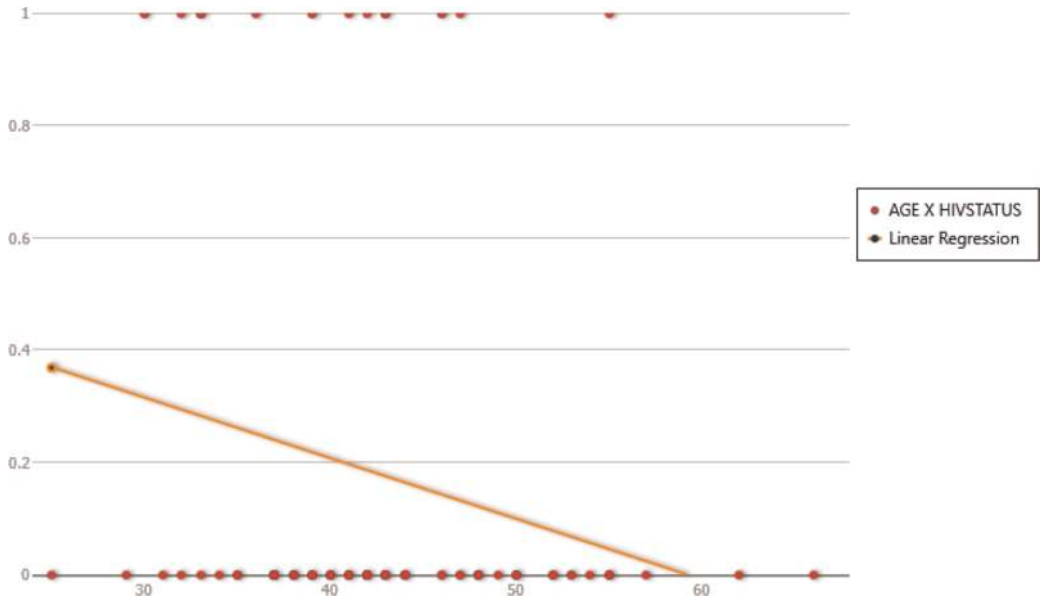

Figure 1.
Serial correlation between HIV serostata and age among women who underwent total abdominal hysterectomy in Dar es Salaam regional referral hospitals, Tanzania (March–October 2017).

HIV serostatus	Single	Married	Widowed	Divorced	Total
HIV seropositive	3	11	0	5	19
HIV seronegative	9	60	9	6	84
Total	12	71	9	11	103[1]

NOTE: *Cochran–Mantel-Hanzel corrected χ^2 value for the association = 8.0176, df = 3.*
[1]N = 107 but 3 individuals refused HIV screening and 1 had discordant HIV results.

Table 1.
Distribution of HIV by marital stata among women who underwent total abdominal hysterectomy in Dar es Salaam regional referral hospitals, Tanzania (March-October 2017).

Variable	Estimates	95% C.I.
Age*	- 0.8156	- 0.7488–0.9970
Marital status**	1.6429	1.3914–1.9216
Intercept	0.449	***

N.B.: *The model fitness was deemed desirable with LR value of 8.1142 and df = 2.*
**Age was coded in a binary fashion with the cut-off of 45 years (average time for natural menopause?) and found to attain linearity with the logit function. Thus, Age < 45 was used as a reference group.*
***Marital status was collapsed to married/non-married in order to attain model specification of linearity with the logit function. Here, non-married was the reference group.*

Table 2.
Findings on the multivariable logistic regression analysis of HIV-stata on ageing among women who underwent total abdominal hysterectomy in Dar es Salaam regional referral hospitals, Tanzania (March-October 2017).

4. Discussion

We detected *a statistically significant association for the probable drop in HIV-risk after age of 45 among hysterectomised women*. The finding translates to an average drop of about 30% in HIV-risk for each annual increase in life expectancy after the age of 45 years. From an evolutionary perspective, our findings are likely to be a reflection of *antagonistic pleiotropy* theory of ageing. It is evident in literature as part of a non-adaptive evolution of ageing process, as per reproductive senescence assumption. However, a word of caution - *it was a statistical estimate, out of secondary data analysis!* We therefore in a pioneering move, call for biologically plausible prospective study designs, to substantiate the exact cause of our current observed statistical puzzle!

By reflecting the nature of our target population, we derived *a possibility for hormonal interplay that potentiate HIV-entry in women during their reproductive age; and significantly drop upon cessation of menses or removal of their endocrine uteri*. Several studies in the past have suggested potential roles of female reproductive hormones in facilitating HI-viral entry and proliferation in female epithelial tissues [22–27]. For instance, Aaron Weinberg and his colleagues showed for the 1st time back in 2003, that HIV-1 induced β-defensin expression in human *oral epithelial cells, with subsequent HIV-1 replication blockage, by the β-defensin 2 & 3, via direct interaction with virions, and also through modulation of CXCR4-tropic* HIV-1 isolates [24]. To our views, Weinsberg's findings were novel even though the target was oral (rather than genital) epithelia [24]. Likewise, Morrison and colleagues performed an individual data 18-prospective studies incorporating 2-stages random effect meta-analysis with 43613 women-years of

follow-up, that resulted to an adjusted Hazard Ratio (aHR) of 1.5 (95% C.I.: 1.24-1.86) upon usage of Depot Medroxyprogesterone Acetate (DMPA) [22]. Morrison study controlled for incident known biological and behavioural risk factors [22]. Progesterone (and not oestradiol) was associated with increased risks in those studies [22, 23, 26, 27]. However, causality has not been established on this topic. We hope our study findings have added quantitative estimates of association between HIV and ageing endocrine processes in non-gravid female humans.

The estimated HIV burden (17.76%) reported in our study is higher than recently reported HIV/AIDS statistics in Tanzanian general population. Tanzania's HIV Impact Survey 2016–2017 reported HIV prevalence of 6.5% among women aged 15–64 years [28]. However, our study population was unlikely to be representative of all women in Tanzania. Another contrasting factor was our limited time of follow-up, in days rather than months or years, normally applied for HIV-seroconversion incidence studies. The zero incidence in HIV-seroconversion rate observed may also likely be a function of limited time of follow-up. Moreover, of special interest to our findings, was the link between removal of endocrine uterus (a marker of *ageing* process) and HIV-risk. On average, a linear association accounted for more than half the variation between HIV-risk and chronological age. Besides, the negative sign in the correlation estimate; signified a probable reduction in HIV-risk with increasing age. It was additional statistical evidence, besides the estimated odds ratio statistic found on the linear model. However, we wish to caution against potentiality for both Berkson's and ecological fallacies when generalizing our findings. We wish our findings to be taken as *a treasure hunt* rather than justifiable evidence at present. For instance, we see a *potential for malice*, upon generalisation of these findings at individual level. We wish to caution readers, that the statistics on reduction in HIV-risk with ageing was analysed at group level. Otherwise, the same finding has several alternative explanations.

First, although the current analysis involved all women who underwent hysterectomies during the study period, and hence the estimate unlikely to be due to sampling variability, we did not have a control group by design. Moreover, there was relatively fewer individuals, in old age (>65 years) category. The analysis was therefore underpowered for detection of the observation among *senior citizens* per se. Middle aged women constituted the majority in our study population. The young and middle age groups are evident to be the most affected by HIV in Tanzania [28]. However, that evidence is doubted in present day Tanzania [29], as HIV has achieved a stable chronic status at community level. Historical data on predominance of young/middle aged members on HIV statistics in Tanzania by their own do not rule out high HIV incidence/prevalence in old aged group. Thus, it is equally likely, that our current findings to be a *statistical artifact* than a real phenomenon. However, the fact that even with the notable *under-powered statistics*, the observation was still statistically significant; is worth *speculations* towards a probable real biological phenomenon. The view follows a common knowledge, that it is relatively difficult to attain statistical significance in under-powered dataset than adequately (over)- powered dataset. We therefore strongly call for biological and clinical research on this specific topic.

Likewise, Tanzania just like other sub-Sahara African countries has never included ≥ 65 years cohort in its national HIV/AIDS surveys. This is for a variety of reasons including assumption of HIV-infection as a disease of youth and young adults. That assumption is considered by authors as a complete myth at present. The reason for disputing that assumption as a myth has been published before [29]. Otherwise, data on HIV-statistics among ≥ 65 years in Tanzania are scanty. Of the few available ones, there is one with evidence that reported a *relatively* low point prevalence (2.1%) [30].

It constituted senior community-dwelling females in North-Eastern Tanzania [30]. Currently, we are hesitant to assume that single retrieved community prevalence study to be nationally representative. Given the obvious gap, it is naturally justified that further population-based studies are needed on this topic.

Moreover, there is a specific call for interventions targeting ageing process, and senior citizens morbid and mortal statistics the world over, to be derived from reliable and valid tools. For instance, there is growing evidence that most scales and indicators used for assessing senior citizens morbid conditions report indices with questionable reliability globally [31]. One member of our team has just published his findings [31], that showed the current global scales and indicators for assessing frailty to record reliability values that were lower than *greatest lower bound* (*glb*) reliability estimate [31]. Part of the challenge has been contributed by years-long tendency of editors and reviewers to consider Chronbach's alpha coefficient as *a sin qua non* for defining reliability index in scientific literature. We could not control all biases associated with our quantitative variables nor did we assume perfection in the literature cited in this chapter, against all systematic and measurement errors in them. The fact that the world is ageing fast, especially sub-Sahara African countries [32], calls for tools with appreciable precision and accuracy during data collection & reporting processes. Thus, studies on biological, clinical, public health, demographic as well as economic analyses of ageing processes are highly warranted globally. Our message given the current statistical findings, *some somatic maintenance properties are likely to be retained (reversed) after reproductive years in female humans!*

Likewise, we took a careful measure not to overlook the finding on HIV and marital stata. There was a rather strong ego to consider that finding as spurious, but indeed the decision was not supported by a logical flow of reasoning among investigators. In fact, we are still debating! Previous studies in similar settings yielded confusing results [33–35], with one study from a population based study in Tanzania that conferred an almost additional 50% risk (aOR: 1.49, 95% C.I.: 1.08–2.04) to remarried couples compared to single/cohabiting partners [35]. Otherwise, the fact that HIV-infection has been present in Tanzania since 1983 [29], and ante-retro viral drugs against HIV became available in mid-1990's [29]; justifies possibilities for residual vertical infection, among infants born with HIV from infected parent(s), to proceed to adulthood. Should this speculation be valid, assumptions related to exclusively acquired HIV risks after sexual maturity could be nullified. Evidently, a member of our research group once co-authored a population based study, among under-fives in a sub-urb of Tanzania, that realized potential sources of infectious ailments, via a domain of febrile illnesses [36]. However, details about the HIV-associated behavioural risks as well as impact of Ante-Retro-Viral drugs against HIV to babies born with the disease were beyond the objective of our current and previous works. Thus, we do believe there is a desperate need for future studies on the mechanisms behind preponderance of HIV infection among participants who reported in married category.

Lastly, much as we do believe our current findings to be reflective of antagonistic pleiotropy theory of ageing process, we wish to address some other important limitations of our findings. It has been a general consensus that women tend to outlive men in longevity studies [37–42]. Even though most scholars of the past (and likely the present?) still associate the reason(s) back to environmental causes [42]; there is a clear indication, that the concept to have an underlying biological and/or clinical causes [37–41]. Mysteriously to our current findings, there have been previous studies that reported female advantages in HIV-survival patterns whether or not on ante-

retroviral treatment in similar settings [43, 44]. Thus, female survival advantages tend to manifest both against HIV-risks as well as in HIV-infection whether or not the latter factor is associated with treatment. Besides, we could not set up an enough time follow-up study in order to arrive with our current conclusion. However, we do believe what we just showed (probably for the first time?) to the world to be an otherwise real biological phenomenon, that has been part of knowledge base in what is currently referred to as biogerontology.

5. Conclusions

There was an observed statistically significant reduced risk of HIV with ageing process in this secondary analysis. None of the studied women seroconverted against HIV during our follow-up period. Point prevalence of HIV among total hysterectomised women was higher than otherwise reported in the Tanzania's general population. Patients reported to be married had a statistically significant higher chance of being HIV-seropositive than others in this study population.

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Conflict of interest

The authors declare no conflict of interest.

Author details

Kelvin Leshabari[1,2*], Godfrey Chale[2,3] and Rashid Salim[3]

1 Ageing Research Group, Registered Trustees of Ultimate Family Healthcare, Dar es Salaam, Tanzania

2 Clinical Research Unit, I-Katch Technology Ltd, Dar es Salaam, Tanzania

3 Department of Obstetrics and Gynaecology, International Medical and Technological University, Dar es Salaam, Tanzania

*Address all correspondence to: kelvin@familyhealth.or.tz; celsius_lx@yahoo.co.uk

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