

Full Length Research Paper

Self-reported adherence to antiretroviral therapy in sub-Saharan Africa: A meta-analysis

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As treatment of HIV infection with antiretroviral medications becomes a reality in sub-Saharan Africa, adherence to treatment regimen becomes a challenge. A meta-analysis was conducted to summarize the reported adherence rate in sub-Saharan Africa. Forest plot was used to visualize the extent of heterogeneity among studies. Following the random effect model, the combined adherence percent was 84.31% (95% CI = 79.48% - 88.60%). The Monte Carlo sensitivity analysis provided an alternative statistical method to evaluate pooled proportion and the analysis was similar to the random effect analysis. Identified barriers to adherence include: depression, centralized ART clinic, interruption in drug supply/procurement, stigma, absence of social support, cost of ART, complacency, forgetfulness and medication related problems. Cost of ART (OR = 2.19; 95% CI= 1.65 – 2.90), Complacency (OR = 5.25; 95% CI = 2.89 – 10.80), and medication related problems (OR = 1.68; 95%CI = 1.28 – 2.22) were the strongest barriers to adherence. This study showed a good level of adherence in sub-Saharan Africa. However, barriers to adherence identified in this study could be employed to improve adherence to a near perfect level.

Key words: Adherence, antiretroviral, Sub-Saharan Africa, HIV/AIDS, self-reported, meta-analysis.

INTRODUCTION

HIV is a major public health problem for developing countries especially those in sub-Saharan Africa. Sub-Saharan Africa is more heavily affected by HIV and AIDS than any other region of the world (UNAIDS, 2013). At the end of 2011, estimate of 23.5 million (69%) people were living with HIV globally in this region with 1.2 million death recorded (UNAIDS, 2012/2013).

Antiretroviral therapy has been shown to improve patients' therapeutic outcome in several studies (Chi and Cantrell, 2009). With the help of donor agencies, the number of patients receiving antiretroviral therapy in sub-Saharan Africa has increased. In Africa, the number of patients on antiretroviral therapy increased from less than 1 million in 2005 to 7.1 million in 2012 (UNAIDS, 2013). As treatment of HIV infection with antiretroviral medications becomes a reality in sub-Saharan Africa, adherence to treatment regimen also becomes a challenge

that needs to be addressed. Although, adherence to ART in some sub-Saharan African countries is over 70%, opportunities remain for improvement to a near perfect level.

Adherence is defined as taking medications or interventions correctly according to prescription (Reda and Biadgilign, 2012). There are different methods of assessing adherence which include: Medication event monitoring (MEM); Self-report; pill count; biologic markers; body fluid assay; viral load monitoring etc (Landovitz, 2011). Pill count, MEM and self-reported method are the most reliable methods (Mweemba et al., 2010). However, there is no gold standard method for measuring adherence. The self-reported method is easier to perform and is cost-effective compared to other methods. A major disadvantage of the self-reported method is that the patients could be bias in their reports. Some studies have shown that antiretroviral regimens require 70-90% adherence in order to effective (Nachega et al., 2010), while most studies have shown that ART requires $\geq 95\%$ adherence in order to be effective (Byakika-Tusiime et al., 2005a; Diabate et al., 2007; Weiser

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et al., 2003). Understanding the pathogenesis of HIV has suggested that adherence to ART of at least 95% or greater is required to keep the viral load at undetectable levels for as long as possible to prevent drug resistance and to maintain the functionality of the immune system. Knowing the percentage of adherence and understanding the predictors of non-adherence are the initial steps in a bid to improve adherence to ART. A detailed understanding of the possible factors that can cause non-adherence will greatly aid in the development of interventions to improve adherence in this African setting.

This study aimed to evaluate the percentage of adherence to antiretroviral therapy (ART) in sub-Saharan Africa from 2003-2012 using the self-reported method, to identify barriers to adherence and strategies to improve adherence.

METHODS

Study Objective

PUBMED and Cochrane library were searched for similar meta-analysis to avoid replication in case the study has been conducted. The Problem-intervention-comparism-outcome (PICO) was used to formulate the research objective but in this analysis, there was no comparism. Only 'problem-intervention-outcome' were used to formulate the research objectives. The objectives of the meta-analysis were: to estimate the percentage of adherence to ART in sub-Saharan Africa based on self-report; to determine and analyze predictors of non-adherence to ART; and to suggest strategies to improve adherence.

Data Sources

The search for primary studies was done by searching published literature using seven general databases and search engines which include PUBMED, MEDLINE, AJOL (African Journal Online), JAIDS (Journal of Acquired Immune Deficiency Syndrome), JIAPAC (Journal of the International Association of Physician in AIDS Care), IJSA (International Journal for STDs and AIDS), AIDSONLINE and Google scholar. The key words (self-reported, adherence, HIV, ART, sub-Saharan Africa, predictors of adherence, barriers of adherence) combined differently were used in the search. Full texts and abstracts of relevant studies were collected.

Study Selection

After identification of relevant studies, each study was assessed for eligibility. The authors searched all the

abstracts and full texts independently against criteria for inclusion. Each article was analyzed individually based on percentage of adherence, objective of study, area of the study, predictors of non-adherence, method, result, implication and recommendation. Full texts or abstracts were retrieved for those that met the inclusion criteria. Studies were included if the study assessed self-reported adherence to ART; if the study was carried out in sub-Saharan Africa; if the study explored factors of medication adherence; If the study was carried out between 2003 – 2012; If the study dichotomized adherences at $\geq 95\%$. For example: an inclusive study is one that dichotomized adherence at $\geq 95\%$ and reports that 52 patients out of 105 patients adhere to their medication, which implies that 52 patients took at least 95% of their medications.

Medication adherence assessed by pill count or MEM only was excluded except where self-reported adherence was inclusive in the study. Studies that dichotomized adherences at $< 95\%$ were excluded. Abstracts and full texts with implicit methodology were also excluded.

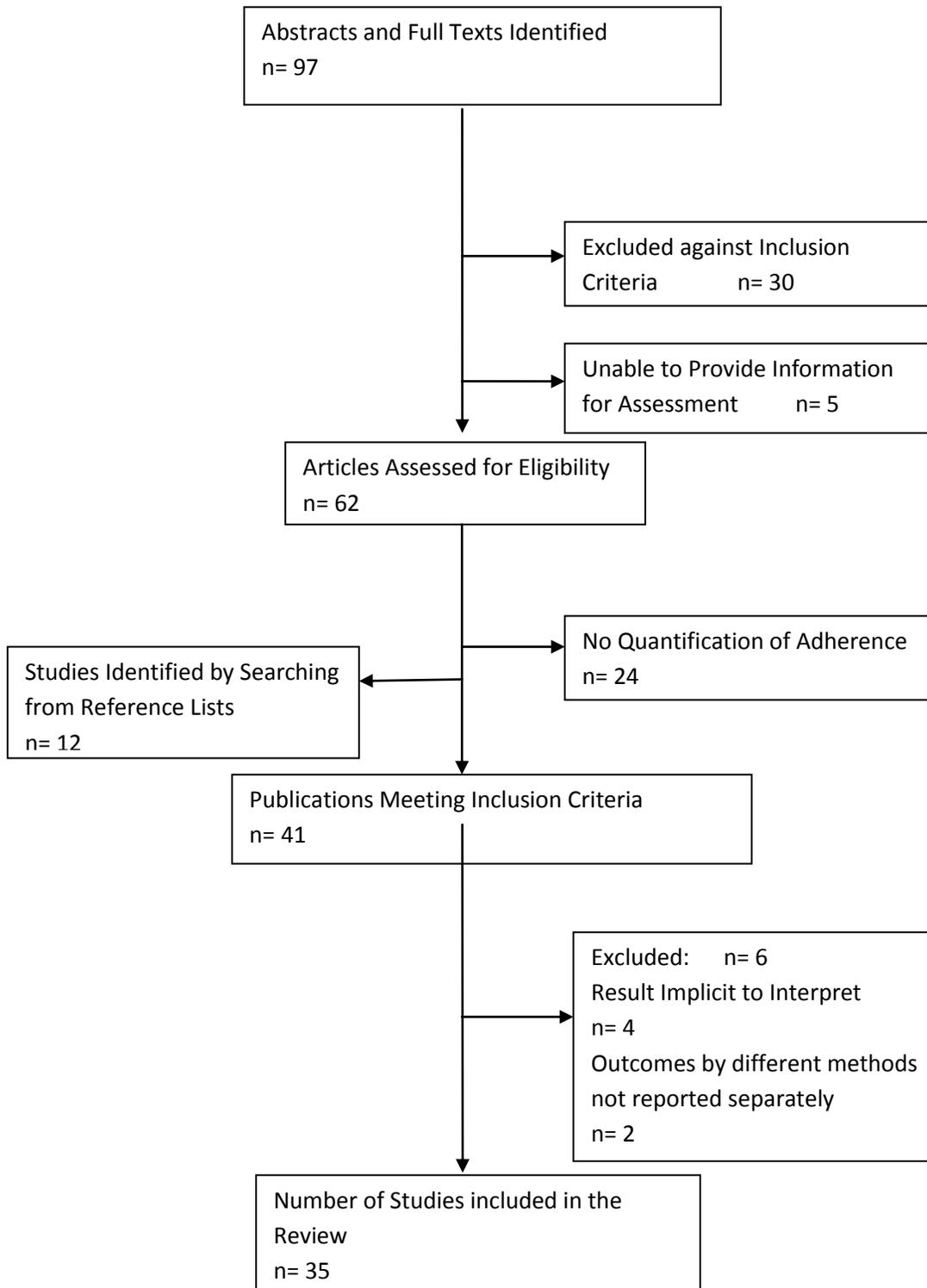
Data Extraction

Reported findings in the selected studies were extracted using the review's extraction form. The extraction was done in duplicate. Information extracted from each study include the following: country of study, author(s), study type, sample size, adherence measure used, reasons for non-adherence, contributing factors to adherence, and percentage of adherence.

Data Synthesis and Analysis

Adherence estimates were presented in a table. A formal meta-analysis was conducted to summarize the reported adherence rates in the individual studies. The primary aim of the meta-analysis was to determine the overall proportion of patients in sub-Saharan Africa that adhere to their ART. Forest plot was used to visualize the extent of heterogeneity among studies. Since heterogeneity was expected, a measure of the degree of inconsistency (I^2) across studies was conducted using Cochrane Q, moment-based estimate of between studies variance and I^2 measure. The I^2 statistic was calculated as a measure of the proportion of the overall variation in adherence that was to between-study heterogeneity (Higgins and Thomas, 2002). The forest plot shows the individual study proportion with Clopper-pearson confidence intervals (CIs) and the overall (combined) Dersimonian-Liard pooled estimate.

Analysis was conducted using Stats Direct statistical software (Stats Direct Ltd, version 2.7.8). Sensitivity analysis was done using Monte Carlo Markov chain simu-

Figure 1. Flow Chart of Study Selection Process.

lation of variability (Briggs et al., 2006; Robert and Casella, 2004). In the sensitivity analysis, the proportions were made probabilistic using beta-distribution. 1000

iterations were used in the simulation. Multivariate logistic regression model was used to analyze the predictors of non-adherence. A column was made for the total popula-

Table 1. Characteristics and Proportions of the Studies.

Source	Country	Study Type	Age (y)	Sample Size	Adherent	Proportion Adherent (95% CI)
Nachegea et al, 2004	South Africa	CS	≥18	66	58	0.88 (0.78-0.95)
Musiime et al, 2011	Rwanda	LS	≥18	389	354	0.91 (0.88-0.94)
Iroha et al, 2010	Nigeria	CS	≤18	212	183	0.86 (0.81-0.91)
Diabate' et al, 2007	Ivory Coast	LS	≥18	591	439	0.74 (0.71-0.78)
Weiser et al, 2003	Botswana	CS	15-49	109	59	0.54 (0.44-0.64)
Okonji et al, 2012	Kenya	LS	≥18	434	366	0.84 (0.81-0.88)
Nabukeera-Barungi et al, 2007	Uganda	CS	2-18	170	152	0.89 (0.84-0.94)
Davies et al, 2008	South Africa	LS	1-5	115	84	0.73 (0.64-0.81)
Rougemont et al, 2009	Cameroun	LS	≥18	238	178	0.75 (0.69-0.80)
Chabikuli et al, 2010	Uganda	CS	≥18	100	71	0.71 (0.61-0.80)
Bajurniwe et al, 2009	Uganda	LS	≥18	175	149	0.85 (0.79-0.90)
Byakika-Tusiime et al, 2005a	Uganda	CS	≥18	304	207	0.68 (0.63-0.73)
Muyingo et al, 2008	Uganda/Zimbabwe	LS	≥18	2957	2785	0.94 (0.93-0.95)
Senkomago et al, 2011	Uganda	CS	18-65	140	140	1.00 (0.97-1.00)
Watt et al, 2010	Tanzania	CS	≥19	340	320	0.94 (0.91-0.96)
Laurent et al, 2004	Cameroun	ORCT	≥18	60	59	0.98 (0.91-1.00)
Adedayo et al, 2005	Nigeria	CS	≥18	579	498	0.86 (0.83-0.89)
Brown et al, 2004	South Africa	CS	≥18	50	38	0.76 (0.62-0.87)
Ferris et al, 2004	South Africa	CS	≥18	74	57	0.77 (0.66-0.86)
Darder et al, 2004	South Africa	LS	≥18	192	168	0.88 (0.82-0.92)
Karcher et al, 2004	Uganda	LS	≤18	76	52	0.68 (0.57-0.79)
Byakika-Tusiime et al, 2005b	Uganda	LS	< or > 1	44	43	0.98 (0.88-1.00)
Hosseinipour et al, 2004	Malawi	LS	≥18	141	134	0.95 (0.90-0.98)
Omes et al, 2004	Rwanda	LS	≥18	95	88	0.93 (0.85-0.97)
Tu et al, 2004	DR Congo	LS	NA	30	30	1.00 (0.88-1.00)
Traore et al, 2004	Burkina Faso	LS	≥18	80	24	0.30 (0.20-0.41)
Ramadhani et al, 2006	Tanzania	CS	19-69	150	127	0.85 (0.78-0.90)

Abbreviations: CS, Cross Sectional; LS, Longitudinal study; NA, Not available
ORCT, Open Randomized Controlled Trial.

tion of each study. Another column represented the number of non-adherent patients. The remaining columns represented the barriers to adherence. A barrier identified in each study is represented by the value '1' or else, zero ('0'). The barriers to adherence were analysed and summarized with the aid of the software.

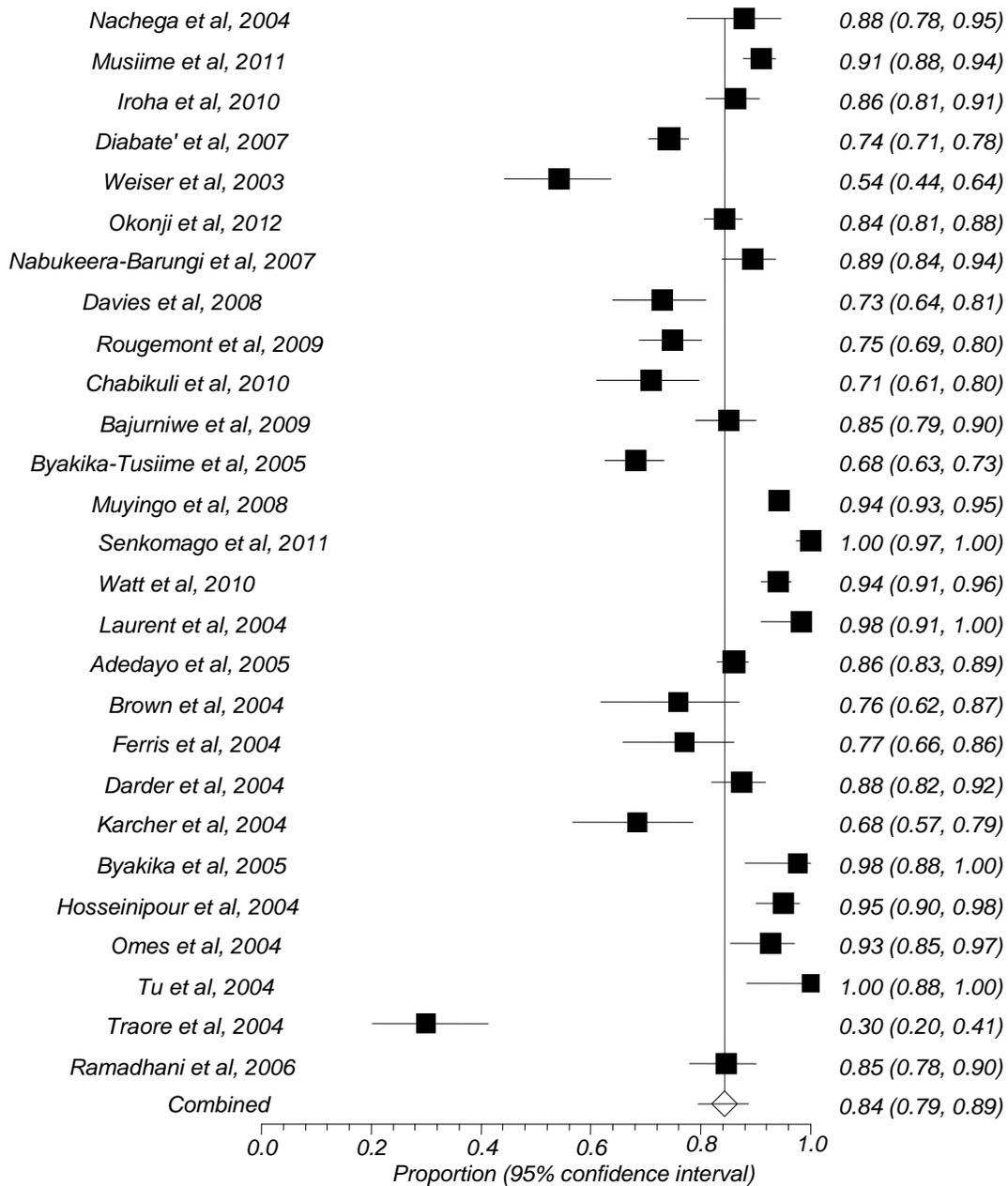
RESULT

Quantification of Adherence

A total of 27 articles (full texts and abstracts) that met the

inclusion criteria out of the 41 relevant studies were used in the meta-analysis. Some studies met the inclusion criteria but had no report on percentage of adherence. Rather, they had reports on predictors of non-adherence. A flow diagram of the studies included in this analysis is shown in figure 1. 13 countries in sub-Saharan Africa had studies on self-reported adherence that were found in electronic data bases.

The adherence rate ranged from a minimum of 30% to a maximum of 100% as shown in table 1. The combined adherence in the analysis showed an adherence of 88.11% (95% CI = 87.39% - 88.81%) in the fixed effect model. For the heterogeneity of studies conducted, the Q

Figure 2. Forest Plot of adherence rate with 95% confidence interval (n = 27).

statistic was very large ($Q = 705.50$, $df = 26$, $P < 0.0001$; $I^2 = 96.3\%$). Since the variation in the studies were very large ($I^2 = 96.3\%$), the random effect model was followed for data analysis. Following the random effect model, the

combined percentage of adherence was 84.31% (95% CI = 79.48% – 88.60%) as shown in figure 2. The Monte Carlo sensitivity analysis provided an alternative statistical method to evaluate the pooled propor-

Table 2. Multivariate Logistic Regression.

Variable	OR	95% CI	Pvalue
Cost of ART	2.19	1.65 – 2.90	0.0001
Complacency	5.25	2.89 – 10.80	0.0001
Medication Related Problems	1.68	1.28 – 2.22	0.0001

OR, Odds Ratio; CI, Confidence Interval.

tion and the analysis was similar to the pooled random effect analysis, 82.25% (95% CI = 81.91% - 82.59%).

Barriers to Adherence

Most of the articles that met the inclusion criteria have been able to show factors that were independently related to poor adherence.

Financial constraint and cost of ART:

Financial constraint is the principal barrier to adherence in Botswana and some other parts of sub-Saharan Africa (Weiser et al., 2003). ART are also very expensive for most Africans. Except with the aid of donor agencies, most HIV patients cannot afford to buy their medication and hence poor adherence. However, the problem of financial constraint and cost of ART has reduced drastically by 2012 when compared to 2003 due to the aid of donor agencies.

Depression

This has been shown to be linked with non-adherence (Ramadhani et al., 2007; Chabikuli et al., 2010; Reda et al., 2012). The patients feel they are useless and meaningless to the society and as such, find no need to comply with their medications. This depression is supported by alcohol consumption.

Centralized ART clinic

In some communities in sub-Saharan Africa, there is only one health centre for ART procurement. This challenge is worsen where the ART clinic is far from the patients' home (Adedayo et al., 2005; Ramadhani et al., 2007). This could prevent some patients from attending scheduled clinic visit.

Interruption in drug supply/procurement

This interruption a times can be the fault of the health care providers when they run out of stock or the fault of

the patients who might fail to go for 'refill' or scheduled clinic visit (Nachega et al., 2004; Diabate et al., 2007; Muyingo et al., 2008).

Complacency

Some patients are not worried about their HIV-infection when their CD4 count and quality of life have increased significantly (Diabate et al., 2007). Adherence has been shown to be lower among patients who have been treated for a longer time, say 1 year, suggesting complacency. This has become a problem among long-term ART treated patients who return to clinic to improve physical and mental functioning because they are less motivated to adhere to their ART due to their improved quality of life.

Stigma

HIV patients who do not want their status to be disclosed find it difficult to tell others of their status for fear of discrimination (Nachega et al., 2004; Bajurniwe et al., 2009; Reda et al., 2012). Stigma of the general knowledge of HIV/AIDS, ART and social or family stigmatization are closely related to poor adherence.

Medication Related Problems

This ranges from large size of pills, high number of daily pills, bad taste, side and adverse effect like skin rash, loss of appetite, hunger, hepatitis, neuropathy etc (Weiser et al., 2003; Hosseinipour et al., 2004; Traore et al., 2004; Diabate et al., 2007; Rougemont et al., 2009). Studies have consistently shown that these problems make it difficult for patients to adhere to their treatment.

Absence of social support

Some patients on ART do not have support groups to address their problems and this affects their adherence (Diabate et al., 2007; Watt et al., 2010).

Forgetfulness

Non-adherence is also linked to patients' forgetfulness. Due to absence of reminders, patients report with no cogent reason that they forgot to take their medications in one or more occasions (Muyingo et al., 2008; Bajunirwe et al., 2009; Traore et al., 2004).

Other minor predictors of non-adherence are age and marital status (Byakika-Tusiime et al., 2005a; Diabate et al., 2007).

Using the Multivariate logistic regression model to analyze the predictors of non-adherence, nine predictors which were statistically significant and independently related to non-adherence was analyzed. Other predictors have no quantification of adherence rate so were not included in the logistic model. From the logistic regression model result, 'depression', 'centralized ART clinic', 'interruption in drug supply/procurement', 'stigma', 'absence of social support' and 'forgetfulness' were dropped out of the model because they have no association with non-adherence. Based on the goodness-of-fit tests (fit and residual option), only 'cost of ART', 'complacency', and 'medication related problem' yielded the co variances. Cost of ART (OR = 2.19; 95% CI: 1.65 – 2.90). Complacency (OR = 5.25; 95% CI: 2.89 – 10.80). Medication related problems (OR = 1.68; 95% CI = 1.28 – 2.22) as shown in Table 2.

DISCUSSION

The result of the review shows that adherence is high in sub-Saharan Africa with a total 6862 out of 7912 patients showing adherence $\geq 95\%$. Using the random effect model, the adherence rate was 84.31% (95% CI = 79.48% – 88.60%). The sensitivity analysis using Monte Carlo simulation gave a result similar to the random effect model, revealing the robustness of the random effect model's result. Predictors of non-adherence analyzed using multivariable logistic regression showed that non-adherence was significantly associated with 'cost of ART', 'complacency' and 'medication related problems' only, since their co-variances were in line with the 'goodness-of-fit', with complacency having the highest odds (5.25). Complacent HIV patients are prone to non-adherence 2.9 to 10.8 times than non-complacent patients. From the result it can be deciphered that if complacency is removed as a barrier to adherence, adherence would increase from 84.31% to 93.3%. The result also showed with 95% confidence that expensive ART medication will result in non-adherence 1.7 to 2.9 times than cheap or affordable ART drugs. It can also be deciphered that expensive ART independently contributed to about 3.8% of non-adherence. Thus if 'cost of ART' as a barrier to adherence is addressed, adherence will increase to 88.1%.

A meta-analysis in 2006 which employed diverse methods and dichotomized adherence at $>80\%$ found out that 77% of patients in sub-Saharan Africa were adherent to their ART, while 55% patients on ART in North America were adherent (Mill et al., 2006). Based on 'Mill et al' result, it can be inferred that there is increase in adherence to ART in sub-Saharan Africa from 2006 to 2012. Although, the study by 'Mill et al' dichotomized adherence at a lower percentage ($>80\%$) and employed other methods besides the self-reported method. Another meta-analysis in 2011, for Spanish patients on Highly Active Antiretroviral Therapy which dichotomized adherence at >90 and employed several methods for measuring adherence showed that 48.7% of the patients were adherent based on self-report with an overall percentage adherence of 55% (Ortego et al., 2011). A recent meta-analysis in 2013 for Indian patients on ART reported adherence of 77% (95% CI = 59% - 81%), (Mhaskar et al., 2013). 50% of the studies use in the analysis by 'Mhaskar et al' reported cost of medication as the most common obstacle for ART adherence in India.

Though the adherence to ART in sub-Saharan Africa is high when compared to other regions of the world, opportunities remain for improvement if certain strategies are implemented. Reminding patients on ART via mobile phone bulk SMS is a feasible approach to improve adherence. Patients can be reminded twice or thrice before their clinic appointment day. They can also be sent SMS every week, even after their clinic visit to ensure they are complying with their medications. Short message like, 'have you taken your ART today?' 'Did you take the complete dose of your ART last week?' can be sent to the patients' mobile phones. This approach saves time, money, ameliorates the problem of complacency and improves adherence. In a randomized controlled trial of text message reminders using mobile phone, there was a high rate of adherence in HIV patients on ART (Pop-Eleches et al., 2011). Patients on ART may have different needs and as such they need specific support group to address their problems. The needs of patients on ART for a long time would vary from the needs of patients who just initiated ART. This will also help to check self-complacent patients. ART should be non-toxic, simple and affordable to address 'medication related problems' and 'cost of ART' challenge. Many patients have reported that the number of drugs in their ART regimen is too much. They also complain of bad taste and toxicity (Weiser et al., 2003; Nachega et al., 2004; Rougemont et al., 2009). The most commonly used and least expensive ART regimen in resource-limited settings especially in sub-Saharan Africa is fixed dose combination of stavudine + lamivudine + nevirapine. Though, stavudine is responsible for irreversible side effect such as peripheral neuropathy, nerve damage in the feet, legs and hands, numbness, tingling, lactic acidosis, diarrhea etc. WHO recommends the phasing out

of stavudine and replacing it with tenofovir or zidovudine. These agents are more expensive, but they are less toxic (UNAIDS, 2012). The WHO integrated management of adult and adolescent illness (IMAI) model has designed simplified ART protocols that makes it easy and possible to delegate some task formerly perform by doctors, to be performed by nurses and some task that were performed by nurses to be performed by community health workers (WHO, 2013). In Human Resource for Health (HRH) limited regions like sub-Saharan Africa, implementing this protocol may also help to improve adherence.

This analysis has some limitations which must be considered in interpretation of the result. There are 44 countries in sub-Saharan Africa from the political point of view and 49 from the geographical point of view. However, only 13 countries had reports on self-reported adherence been found in the databases. Though, these 13 countries had a total of 27 articles on the rate of self-reported adherence. So no data was found in over 2/3 of the sub-Saharan African countries. The authors aimed to reduce biasness and complexity in methodology, by using only studies on self-reported method of adherence which excludes many studies that used alternate methods, resulting to smaller sample size.

There was no uniform period of time for which adherence was measured. The studies assessed adherence at different time duration. Some studies were longitudinal while some were cross-sectional. Also, the population analysed is not homogenous, involving different age groups and sex.

CONCLUSION

This study shows a high level of adherence in sub-Saharan Africa which should be improved or sustained. Future studies should assess self-reported adherence in regions of sub-Saharan Africa where none have been carried out. More attention should be paid to barriers of non-adherence and strategies to improve adherence should be implemented in areas where no significant effort has been made to improve adherence. Non-adherence should be detected earlier via reliable strategies to avoid viral mutation and drug resistance.

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CONFLICT OF INTEREST

Funding for this research was provided by C.E. Okafor and

O. I. Ekwunife. The authors declare no conflict of interest.

AUTHORS CONTRIBUTION

OIE formulated the research question. CEO gathered data (full text, abstract, software and other tools). CEO assessed the studies against criteria for inclusion. Data extraction was done by CEO and OIE independently. Data synthesis and analysis was done by CEO. CEO wrote the first draft of the manuscript. OIE reviewed and made contributions to the draft. OIE and CEO reviewed the final draft of the manuscript.

REFERENCES

- Adedayo A, Modupeola A, Timothy A (2005). Scaling up Antiretroviral Therapy use for HIV-positive Adults in Southwestern Nigeria. Presented at: 12th Conference on Retroviruses and Opportunistic Infections; February 22-25; Boston, Mass. Abstract A623.
- Bajunirwe F, Arts EJ, Tisch DJ, King CH, Debanne SM, Sethi AK (2009). Adherence and Treatment in HIV-1 Infected Adults Receiving Antiretroviral Therapy in Rural Government Hospital in Southwestern Uganda. *JIA PAC*. (8): 139-147.
- Briggs A, Claxton K, Sculpher M (2006). *Decision Modeling for Health Economic Evaluation*. New York. Oxford University Press. Inc.
- Brown S, Friedland GH, Bodasing U (2004). Assessment of Adherence to Antiretroviral Therapy in HIV-infected South African Adults. Presented at: XV International AIDS Conference; July 11-16; Bangkok. B12223.
- Byakika-Tusiime J, Oyugi JH, Tumwikirize WA, Katabira ET, Mugenyi PN, Bangsberg DR (2005a). Adherence to HIV Antiretroviral Therapy in HIV Positive Ugandan Patients Purchasing Therapy. *International journal for STD and AIDS*. (16): 38-41.
- Byakika-Tusiime J, Oyugi J, Musoke P, Ragland K, Bangsberg DR. (2005b). Adherence approaches 100% with excellent viral load suppression when all HIV-infected Ugandan household members receive antiretroviral treatment. Presented at: 12th Conference on Retroviruses and Opportunistic Infections; February 22-25; Boston, Mmass. Abstract: A626.
- Chi BH, Cantrell RA (2009). Adherence to First-line Antiretroviral Therapy affects non-virologic outcomes among Patients on Treatment more than 12months in Lusaka, Zambia. *Int. J. Epidemiol*. 38(3): 746-756.
- Chabikuli NO, Datonye DO, Nachega J, Ansong D (2010). Adherence to Antiretroviral Therapy, Virologic Failure and Workload at the Rustenburg Provincial Hospital. *SA Fam Pract*. 52(4): 350-355.
- Darder M, Michaels D, Boulle A, Ncobo N, MacLean E, Goemaere E (2004). Determinants of short and long term

- adherence to antiretroviral treatment in resource-poor settings. Presented at: XV International AIDS Conference; July 11-16; Bangkok. Abstract B11852.
- Davies M, Boulle A, Fakir T, Nuttall J, Eley B (2008). Adherence to Antiretroviral Therapy in Young Children in Cape Town, South Africa, Measured by Medication Return and Care-givers Self-report: A Prospective Cohort Study. *BioMed Central Paediatrics*. (8): 34.
- Diabate S, Alary M, Koffi CK (2007). Determinants of Adherence to Highly Active Antiretroviral Therapy among HIV-1 Infected Patients in Ivory Coast. *AIDSONLINE*. 21(13): 1799-1803.
- Ferris D, Dawood H, Chiasson MA, Diamond B, Hammer SM (2004). Self-reported Adherence to Antiretroviral Therapy and Virologic Outcomes in HIV-infected Persons in Durban, KwaZulu Natal, South Africa. Presented at: XV International AIDS Conference, July 11-16; Bangkok. Abstract WePeB5829.
- Higgins JP, Thomas SG (2012). Quantifying Heterogeneity in a Meta-Analysis. *Stat. Med.* (21): 1539-1558.
- Hosseinipour MC, Kanyama C, Nkhalamba T, Phiri S, Weigel R, Funsani C, Potani C, Namakwa D, Lugalia L, Van der Horst C, Hoffman I, Neuhann F (2004). Safety and efficacy of D4T/3TC/NVP among HIV positive adults in Lilongwe, Malawi. Presented at: eJ. Int. AIDS Soc. Meeting; July 11-16; Abstract: TuPeB4522.
- Iroha E, Esezobor CI, Ezeaka C, Temiye EO, Akinsulie A (2010). Adherence to Antiretroviral Therapy among HIV-infected Children Attending a Donor-funded Clinic at a Tertiary Hospital in Nigeria. *Afri. J. AIDS Res. AJOL*. 9(1): 25-30.
- Karcher H, Moses A, Weide AL, Stelzenmueller J, Mayer A, Harms G (2004). Evaluation of Antiretroviral Treatment in Fort Portal, Western Uganda. Presented at: eJ. Int. AIDS Soc. Meeting; July 11-16; Abstract: B12706.
- Landovitz RJ (2011). What's the Best Way to Measure ART Adherence? *J. Watch*. 23(3).
- Laurent C, Kouanfak C, Koulla-Shiro S, Nkoue N, Bourgeois A, Calmy A, Lactuock B, Nzeusseu V, Mougnotou R, Peytavin G, Liegeois F, Nerrienet E, Tardy M, Peeters M, Andrieux-Meyer I, Zekeng L, Kazatchkine M, Mpoudi-Ngole E, Delaporte E (2004). Effectiveness and Safety of a Generic-fixed-dose Combination of Nevirapine, Stavudine and Lamivudine in HIV-1 Infected Adults in Cameroun. *Lancet*. (364): 29-3.
- Mhaskar R, Alandikar V, Emmanuel P, Djulbegovic B, Patel S, Patel A, Naik E, Mohapatra S, Kumar A (2013). Adherence to Antiretroviral Therapy in India: A Systematic Review and Meta-analysis. *Indian J Community Med*. 38(2): 74-82.
- Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, Rachlis B, Wu P, Cooper C, Thabane L, Wilson K, Guyatt GH, Bangsberg DR (2006). Adherence to Antiretroviral Therapy in Sub-Saharan and North America. *JAMA*. (296): 679-690.
- Musiime S, Muhairwe F, Rutagengwa A, Mutimura E, Anasthos K, Hoover DR, Qiuhu S, Munyazesa E, Emile I, Uwineza A, Cowan E (2011). Adherence to Highly Active Antiretroviral Treatment in HIV Infected Rwandan Women. *PLoS One*. 6(11).
- Muyingo SK, Walker AS, Ried A, Munderi P, Gibb DM, Ssali F, Levin J, Katabira E, Gilks C, Todd J (2008). Patterns of Individual and Population-level Adherence to Antiretroviral Therapy and Risk Factor for Poor Adherence in the First Year of the DART Trial in Uganda and Zimbabwe. *JAIDS*. 48(4): 468-475.
- Mweemba P, Makukula MK, Mukwato PK, Makoleka MM (2010). Quality of Life and Adherence to Antiretroviral Drugs. *Med. J. Zambia*. 37(1).
- Nachega JB, Stein DM, Lehman DA, Hlatshwayo D, Mothopeng R, Chaisson RE, Karstaedt AS (2004). Adherence to Antiretroviral Therapy in HIV-infected Adults in Soweto, South Africa. *AIDS Research and Human Retroviruses*. 20(10): 1053-1056.
- Nachega JB, Mills EJ, Schechter M (2010). Antiretroviral Therapy Adherence and Retention in Care in Middle Income Countries: Common Status of Knowledge and Research Priorities. *Current Opinions in HIV and AIDS*. 5(1): 70-77.
- Nabukeera-Barungi N, Kalyesubula I, Kekitiinwa A, Musoke P (2007). Adherence to Antiretroviral Therapy in Children Attending Mulago Hospital, Kampala. *Annals of Tropical Paediatrics: International Child Health*. 27(2): 123-131(9).
- Okonji JA, Zeh C, Weidle PJ, Williamson J, Akoth B, Masaba RO, Fowler MG, Thomas TK (2012). CD4, Viral Load Response and Adherence among Antiretroviral Naïve Breast-feeding Women Receiving Triple Antiretroviral Prophylaxis for Prevention of Mother-to-child-Transmission of HIV in Kisumu, Kenya. *J. Acquir. Defic. Syndr.* 61(2): 249-257.
- Omes C, Schuman M, Kamesigwa J, Demeester R, Mukakalisa J, Parisel A, Kayibanda E, Arendt C (2004). Adherence to antiretroviral (ARV) therapy among advanced-stage, indigent patients in the funded ESTHER programme in Kigali, Rwanda. Presented at: XV International AIDS Conference; July 11-16; Bangkok. Abstract B12315.
- Ortego C, Huedo-Medina TB, Vejo J, Llorca FJ (2011). Adherence to Highly Active Retroviral Therapy in Spain: A Meta-Analysis. *Elsevier Espana*. 25(4): 282-289.
- Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, de Walque D, Mackeen L, Haberer J, Kimaiyo S, Sidle J, Ngare D, Bangsberg DR (2011). Mobile Phone Technologies Improve Adherence to Antiretroviral Treatment in Resource-Limited Settings. A Randomized Control Trial of Text Message Reminder. *AIDSONLINE*. 25(6): 825-834.
- Ramadhani HO, Thielman NM, Landman KZ, Ndosi EM, Gao F, Kirchherr JL, Shah R, Shao HJ, Morphet SC, McNeill JD, Shao JF, Bartlett JA, Crump JA (2007).

- Predictors of Incomplete Adherence, Virologic Failure and Antiretroviral drug Resistance among HIV-Infected Adults Receiving Antiretroviral Therapy in Tanzania. *Clinical Infectious Disease*. 45(11): 1492-1498.
- Reda AA, Biadgilign S (2012). Determinants of Adherence to Antiretroviral Therapy among HIV-infected Patients in Africa. *AIDS Res Treat*. 2012:574656.
- Robert CR, Casella G (2004). Monte Carlo statistical methods. 2nd ed. New York, NY: Springer-verlag.
- Rougemont M, Stoll BE, Elia N, Ngang P (2009). Antiretroviral Treatment Adherence and its Determinants in Sub-Saharan Africa: A Prospective Study at Yaoundé Central Hospital, Cameroun. *AIDS Research and Therapy*. (6): 21.
- Senkomago V, Guwattude G, Breda M, Khoshnood K (2011). Barriers to Antiretroviral Adherence in HIV-Positive Patients Receiving Free Medication in Kayunga, Uganda. *AIDS Care*. 23 (10): 1246-1253.
- Traore AA, Nguyen VK, Fakoya A, McCarrick P, Dhaliwal M, Tioendrebeogo I, Ilboudo A. (2004). Barriers to adherence to ARV therapy in a community-based cohort in Burkina Faso. Presented at: XV International AIDS Conference; July 11-16; Bangkok. Abstract: WePeB5824.
- Tu D, Kos N, Culbert H, Migabo K, Amisi T (2004). ARV selection criteria and innovative group adherence counseling in Bukavu, Democratic Republic of Congo-Program implementation in the context of chronic war and a failing healthcare system. Presented at: XV International AIDS Conference; July 11-16; Bangkok. Abstract B12702.
- UNAIDS Program on HIV/AIDS (2012). UNAIDS World AIDS Day Report: UNAIDS Fact Sheet, 2012. Kaiser Family Foundation.
- UNAIDS Program on HIV/AIDS (2013). Update Report on the AIDS Response in Africa. Geneva, Switzerland.
- Watt MH, Maman S, Golin CE, Earp JA, Eng E, Bangdiwala SI, Jacobson M (2010). Factors Associated with Self-reported Adherence to Antiretroviral Therapy in a Tanzanian Setting. *AIDS Care*. 22 (3): 381-389.
- Weiser S, Wolfe W, Bangsberg D, Thior I, Gilbert P, Makhema J, Kebaabetswe P, Dickenson D, Mompoti K, Essex M, Marlink R (2003). Barriers to Antiretroviral Adherence for Patients Living with HIV Infection and AIDS in Botswana. *J. Acquir. Immune Defic. Syndr*. 34 (3): 281-288.
- WHO Integrated Management of Adolescent and Adult Illness (IMAI), (2004). <http://www.who.int/3by5/publications/documents/imai/en/>. Accessed 21 February, 2013.

Sensitive Analysis.

Study	Live	Probabilistic	Deter	Alpha	Beta
1	0.883906	0.88390553	0.878788	58	8
2	0.909268	0.909268156	0.910026	354	35
3	0.870815	0.870815039	0.863208	183	29
4	0.70742	0.707419515	0.742809	439	152
5	0.537185	0.537184954	0.541284	59	50
6	0.838748	0.838748008	0.843318	366	68
7	0.936581	0.936580777	0.894118	152	18
8	0.772577	0.772576809	0.729508	84	31
9	0.720162	0.720161796	0.747899	178	60
10	0.743971	0.743971348	0.71	71	29
11	0.863541	0.863540739	0.851429	149	26
12	0.707625	0.707624912	0.680921	207	97
13	0.942652	0.942651808	0.941833	2785	172
14	0.991884	0.991883785	1	140	0.5
15	0.960696	0.96069628	0.941176	320	20
16	0.975922	0.97592175	0.983333	59	1
17	0.864777	0.864776805	0.860104	498	81
18	0.838483	0.838483453	0.76	38	12
19	0.690978	0.690978289	0.77027	57	17
20	0.913278	0.913278461	0.875	168	24
21	0.685856	0.685855508	0.684211	52	24
22	0.997041	0.997040927	0.977273	43	1
23	0.96887	0.968870431	0.950355	134	7
24	0.915793	0.915792644	0.926316	88	7
25	0.997442	0.997442096	1	30	0.5
26	0.3199	0.319899797	0.3	24	56
27	0.845333	0.845332563	0.84	126	24
Combined	0.869968	0.86996825	0.843105	6862	1050
				Total	7912

PROPORTION SHEET

	Study										
	1	2	3	4	5	6	7	8	9	10	11
Trial	0.751205	0.92535	0.807779	0.757943	0.480875	0.842334	0.902846	0.70855	0.748298	0.69811	0.882519
1	0.88864	0.909838	0.90901	0.757231	0.50719	0.858647	0.882537	0.710489	0.755316	0.628327	0.862059
2	0.83772	0.921874	0.888831	0.76037	0.619853	0.827235	0.866246	0.738255	0.680635	0.762593	0.834282
3	0.935871	0.930576	0.8498	0.75825	0.574235	0.862477	0.864315	0.673747	0.748169	0.709412	0.89294
4	0.876187	0.906221	0.884511	0.753229	0.54792	0.855093	0.908669	0.747927	0.801369	0.804082	0.866882
5	0.836819	0.923715	0.858538	0.728223	0.542878	0.844896	0.883956	0.720841	0.770982	0.673714	0.827043
6	0.875097	0.889352	0.874124	0.731302	0.486356	0.847089	0.870762	0.683764	0.73516	0.705904	0.871084
7	0.899861	0.90486	0.900324	0.732794	0.534324	0.852333	0.873382	0.757821	0.784546	0.812335	0.852397
8	0.875678	0.895537	0.850085	0.743278	0.551941	0.841793	0.900964	0.694493	0.779106	0.717804	0.825589
9	0.952719	0.897461	0.860508	0.732387	0.409557	0.829371	0.896732	0.731487	0.738186	0.699125	0.832444
10	0.863951	0.899073	0.875455	0.754797	0.4712	0.842219	0.888706	0.700332	0.748515	0.763697	0.854515
11	0.874375	0.870017	0.846698	0.721347	0.508483	0.824537	0.887706	0.663631	0.743931	0.655576	0.841575
12	0.896313	0.920219	0.867836	0.733506	0.542714	0.867483	0.930175	0.708821	0.778839	0.662505	0.870501
13	0.837515	0.925225	0.861312	0.772426	0.543152	0.863372	0.918533	0.768698	0.763303	0.736937	0.851465
14	0.879856	0.924745	0.852372	0.709506	0.48636	0.842596	0.875947	0.678847	0.753443	0.741632	0.888322
15	0.824037	0.923774	0.880758	0.734118	0.595642	0.834652	0.912539	0.785926	0.721689	0.753553	0.876165
16	0.912025	0.909793	0.864213	0.747439	0.41354	0.819035	0.877389	0.698287	0.751856	0.778308	0.891383
17	0.845184	0.90981	0.847333	0.752678	0.514416	0.838271	0.90086	0.657424	0.772174	0.681153	0.845395
18	0.874345	0.894113	0.856041	0.760809	0.477055	0.842276	0.895266	0.795091	0.722506	0.678444	0.883363
19	0.844157	0.889251	0.878469	0.74336	0.507862	0.8415	0.899334	0.661597	0.746476	0.665462	0.87457
20	0.915393	0.91188	0.892466	0.744995	0.525485	0.856204	0.90455	0.681119	0.803867	0.72947	0.857684
21	0.805192	0.898278	0.817288	0.754415	0.594667	0.822652	0.895312	0.694659	0.722577	0.700832	0.846913
22	0.903259	0.912812	0.882789	0.7281	0.445419	0.853215	0.880186	0.752088	0.773248	0.658954	0.804137
23	0.914799	0.89116	0.822423	0.749609	0.681313	0.842515	0.93538	0.761495	0.700535	0.686457	0.865525
24	0.942532	0.932253	0.855816	0.750511	0.559605	0.842187	0.913855	0.767986	0.779194	0.709615	0.78706
25	0.872678	0.933097	0.831208	0.739508	0.546167	0.823067	0.902832	0.734638	0.75991	0.687376	0.864006
26	0.908256	0.928342	0.853359	0.74439	0.600847	0.84109	0.891091	0.716507	0.737992	0.65384	0.857432
27	0.841875	0.932677	0.842973	0.73933	0.547022	0.835367	0.923731	0.622168	0.711982	0.698909	0.837822
28	0.926101	0.907169	0.853491	0.734144	0.538193	0.869335	0.902868	0.669147	0.727541	0.715069	0.860485
29	0.832858	0.912574	0.829866	0.725156	0.55284	0.86751	0.860901	0.762603	0.72409	0.737864	0.867197
30	0.842082	0.906384	0.862039	0.722431	0.485923	0.868198	0.908015	0.726514	0.758082	0.763429	0.86302
31	0.929114	0.919896	0.849522	0.768944	0.639894	0.854169	0.873804	0.694987	0.691015	0.78095	0.895282
32	0.879886	0.900592	0.888208	0.753761	0.557804	0.839123	0.905399	0.738074	0.717587	0.775511	0.836969
33	0.91673	0.935908	0.859576	0.712561	0.557086	0.850971	0.929354	0.707247	0.701699	0.730217	0.884625
34	0.855014	0.897568	0.856725	0.73843	0.562795	0.874455	0.917028	0.716793	0.770736	0.697952	0.839158
35	0.879115	0.91717	0.879656	0.742506	0.528001	0.848876	0.897467	0.729003	0.739048	0.748949	0.858271
36	0.924923	0.898861	0.894677	0.745835	0.488187	0.85376	0.898493	0.728562	0.742024	0.738912	0.829174
37	0.876126	0.90523	0.845047	0.745531	0.497218	0.857315	0.882813	0.75479	0.767757	0.633742	0.868905
38	0.923237	0.898425	0.897474	0.732025	0.503924	0.827457	0.866091	0.680517	0.734812	0.710378	0.841222
39	0.811375	0.892471	0.868827	0.74674	0.558731	0.859337	0.895092	0.793768	0.764044	0.752386	0.812836
40	0.848471	0.912371	0.838201	0.73211	0.606263	0.835938	0.901157	0.720203	0.742135	0.684898	0.812183
41	0.892793	0.876429	0.838026	0.76496	0.635215	0.83382	0.861906	0.737336	0.733897	0.730745	0.828984
42	0.886171	0.929277	0.870634	0.758165	0.537398	0.8767	0.873935	0.695759	0.723531	0.741428	0.78308

