KU LEUVEN

FACULTY OF MEDICINE

The impact of community health workers on HIV therapy outcome in sub-Saharan Africa

Master Thesis proposed to achieve the degree of master in medicine by

Michielsen LOTTE

Unit: Laboratory for Clinical and Evolutionary Virology (Rega Institute)

Department: Microbiology, Immunology and Transplantation

Promotor: Prof. dr. Vandamme ANNE-MIEKE
Mentor: PhD. Kiekens ANNELEEN

KU LEUVEN

FACULTY OF MEDICINE

Leuven, 2017-2018

"*This master's thesis is an exam document. Possibly assessed errors were not corrected after the defense. In publications, references to this thesis may only be made with written permission of the supervisor(s) mentioned on the title page.*"

KU LEUVEN

FACULTY OF MEDICINE

The impact of community health workers on HIV therapy outcome in sub-Saharan Africa

Master Thesis proposed to achieve
the degree of master in medicine by

Michielsen LOTTE

Unit: Laboratory for Clinical and Evolutionary Virology (Rega Institute)

Department: Microbiology, Immunology and Transplantation

Promotor: Prof. dr. Vandamme ANNE-MIEKE
Mentor: PhD. Kiekens ANNELEEN

KU LEUVEN

FACULTY OF MEDICINE

COVER LETTER

Dear Sir/Madam, editor in chief,

Over the past decennia, there has been renewed interest in community health worker (CHW) programs in HIV care in sub-Saharan Africa. It is widely assumed that CHW interventions are not inferior to standard of care (SOC) in terms of antiretroviral therapy outcome, but little high-quality evidence on large-scale CHW interventions is available. Furthermore, it is unclear which specific tasks CHWs need to fulfil in order to maximize the success of HIV treatment outcome.

In this literature review, we summarize the evidence that CHWs interventions are indeed not inferior to SOC and might even be beneficial. Additionally, we analysed various CHW tasks and we found indications that delivering ART, providing individual adherence support and conducting frequent home visits were predictive of a successful CHW intervention, defined as improved therapy outcome compared to SOC or reaching 90 percent of treated patients being virally suppressed. Further research is needed to be able to judge whether any single task or a particular combination of tasks is significantly correlated with a successful CHW intervention, or whether such tasks are context specific.

We feel our review brings a new perspective by focussing on treatment outcome and the specific tasks of CHWs, in the broader context of CHW programs, and we kindly ask you to consider its publication for a broader audience.

Sincerely,

Lotte Michielsen

ABSTRACT

Introduction

In sub-Saharan Africa, the burden on HIV care givers is high. This resulted in renewed interest in community health worker (CHW) programs. We conducted a review of the literature to summarize CHWs' effects on HIV therapy outcome. We also investigated which CHW tasks might favourably impact treatment outcome.

Methods

We conducted a comprehensive literature search in PubMed, Web of Science and Embase for papers published up to October 2018. Included studies were conducted on HIV-positive adults in sub-Saharan Africa and reported biological HIV outcomes. We systematically collected data on HIV therapy outcome and CHW tasks. We used Bayesian network modelling for the analysis of CHW tasks.

Results

We included 19 studies in total: 4 randomized controlled trials, 8 comparative cohort studies and 7 single arm interventions. In all studies, CHW interventions were beneficial or not inferior to standard of care (SOC). The more common tasks of CHWs involved an important human support component, with home visits being the most common task. Upon analysis we found indications that ART delivery, individual adherence support and frequent home visits were predictive of a successful CHW intervention, defined as improved therapy outcome compared to SOC or reaching 90 percent of treated patients being virally suppressed.

Conclusions

We found that CHW interventions are not inferior to SOC and might even be beneficial. We hypothesize that ART delivery, individual adherence support and frequent home visits are predictive of a successful CHW intervention. Further research is needed to be able to judge whether any single task or a particular combination of tasks is significantly correlated with a successful CHW intervention, or whether such tasks are context specific.

Evidence before this study

Over the past decennia, there has been renewed interest in community health worker (CHW) programs in HIV care in sub-Saharan Africa. It is widely assumed that CHW interventions are not inferior to standard of care (SOC) in terms of antiretroviral therapy outcome, but little high-quality evidence on large-scale CHW interventions is available. In two reports, the WHO stresses the importance of community level interventions for people living with HIV. In the context of HIV and AIDS, CHWs are commonly trained to fulfil tasks in prevention, counselling, treatment support and care[4]. However, it is unclear which exact tasks of CHWs are most beneficial to improve HIV treatment outcome[13,14].

Added value of this study

With our literature review, we add evidence to the assertion that CHW interventions are not inferior to SOC. Further, we aimed to document which tasks of the CHWs are most beneficial. Although we did not find evidence for a single task or combination of tasks to correlate significantly with better HIV therapy outcome, we present indications that ART delivery, individual adherence support and frequent home visits are the most important contributions of CHWs to improve biological treatment outcomes of HIV-patients.

KORTE SAMENVATTING

Introductie

De werklast voor HIV-gezondheidswerkers in sub-Saharisch Afrika is bijzonder hoog. Dit leidde tot een hernieuwde interesse in lokale gezondheidsmedewerkers (LGW). We voerden een literatuuronderzoek uit naar de bijdrage van LGWs aan het succes van anti-HIV-therapie. We onderzochten ook welke LGW-taken een positieve impact zouden kunnen hebben op therapie uitkomst.

Methoden

We deden een uitgebreide zoekopdracht in PubMed, Web of Science en Embase naar artikels gepubliceerd tot en met oktober 2018. De geïncludeerde studies hadden betrekking op volwassenen met HIV in sub-Saharisch Afrika en rapporteerden therapie succes op basis van biologische parameters. We verzamelden data rond het resultaat van therapie en LGW-taken op een systematische manier.

Resultaten

We includeerden 19 studies in totaal: 4 gerandomiseerde onderzoeken met controlegroep, 8 vergelijkende cohortstudies en 7 implementatie studies. In alle studies was de impact van LGWs' interventies voordeliger dan of niet inferieur aan de standaard gezondheidsinterventies. De meest uitgevoerde taken omvatten een belangrijke sociale ondersteunende component, met het brengen van huisbezoeken als meest frequente taak. Bij analyse van de LGW-taken vonden we aanwijzingen dat het bezorgen van antiretrovirale medicatie, het individueel ondersteunen van medicatietrouw en het frequent brengen van huisbezoeken voorspellers waren voor een succesvolle LGW-interventie, gedefinieerd door verbeterde therapie uitkomst in vergelijking met standaard gezondheidsinterventies of door het bereiken van minstens 90 percent virale suppressie bij patiënten onder behandeling.

Conclusie

We toonden aan dat LGWs niet inferieur zijn aan de standaard gezondheidsinterventies en zelfs voordelig kunnen zijn. We vermoeden dat het bezorgen van antiretrovirale medicatie, het individueel ondersteunen van medicatietrouw en het frequent brengen van huisbezoeken voorspellers zijn voor een succesvolle LGW-interventie. Meer onderzoek is nodig om te kunnen oordelen of een bepaalde taak of een bepaalde combinatie van taken significant gecorreleerd is met een succesvolle LGW-interventie, of dat dergelijke taken context specifiek zijn.

INTRODUCTION

In sub-Saharan Africa (SSA), 25 700 000 people are living with HIV. This corresponds to 70% of all people living with HIV in the world. In 2014, UNAIDS published the 90-90-90 goals, defining 3 targets by 2020: 90% of all people living with HIV must know their status, 90% of all people with diagnosed HIV infection must receive sustained antiretroviral therapy (ART), and 90% of all people receiving ART must have viral suppression. By 2017, eastern and southern Africa reached 81%, 66% and 52% for those targets, while western and central Africa reached 48%, 40% and 29% respectively. In comparison, western and central Europe and North America reached 85%, 76% and 65% of the three targets in 2016[1].

Over the last decennia, the rapid scale-up of HIV testing and treatment proved instrumental on the road to the 90-90-90 goals, but the health care services in many SSA countries became overstretched[2]. The majority of SSA countries has a physician/population density of less than 0.5 per 1000[3]. This leaves health care staff with little time and resources to invest in patient-centred care. Nevertheless, patients with HIV often require substantial support from their health care provider to achieve optimal therapy outcomes. They need to be retained in care for their whole life and need to adhere to daily ART, a huge challenge for many patients.

As a response to the health worker shortage, there has been renewed interest in community health worker (CHW) programs[2]. The phenomena of CHWs emerged in the mid-1950s, when community members were used to render basic health services to their communities. In the early days, a CHW was not only a healthcare provider, but also acted as an advocate for his or her community. Although nowadays CHWs are mainly focusing on health issues, their strong link with the community is still of major importance for their successful implementation[4]. A comprehensive description for their relation with the community was given by Giblin[5]: *'Indigenous qualities include, in most general terms, the possession of the social, environmental, and ethnic qualities of a subculture and, in more specific terms, a sharing with a client of a verbal and nonverbal language, an understanding of a community's health beliefs and barriers to health care services, and an enhanced empathy with, and responsibility towards a community and its health service needs.'* CHWs are sometimes referred to as 'cultural brokers', since they understand the sociocultural norms of the communities. As such, they can act as intermediaries between the communities and the health sector[6].

At present, there is a wide range of CHWs with an even bigger variety in health related tasks[4]. Depending on the country, these tasks generally include: home visits, environmental sanitation, provision of water supply, first aid and treatment of simple and common ailments, health education, nutrition and surveillance, maternal and child health and family planning activities, communicable disease control, community development activities, referrals, record-keeping, and collection of data on vital events[7]. In the context of HIV and AIDS, CHWs are commonly trained to fulfil tasks in prevention, counselling, treatment support and care[4].

The positive impact of CHW programs on ART outcome in SSA is widely assumed[8]. Additionally, several recent reviews stress that optimizing existing services, such as CHW programs, are a promising way to improve adherence to ART[9–12]. However, little high-quality evidence on large-scale CHW interventions is available[4]. In two reports, the WHO stresses the importance of community level interventions for people living with HIV. Yet, it is unclear which exact tasks the CHWs need to fulfil[13,14]. It is important to look at existing programs to learn what does or does not work. Identifying why some CHW interventions are successful and others are not, is of major importance to achieve optimal health care contribution by CHWs.

We conducted a review of the literature to synthesize the effects on HIV therapy outcome of various CHW programs implemented in SSA to date. Our primary aim was to document the current knowledge on whether CHWs can contribute to improved HIV therapy outcome in SSA. Second, we aimed to investigate which tasks are commonly assigned to CHWs, and which CHW interventions might favourably impact treatment outcome. As such, this literature review focuses on the last goal of the UNAIDS 90-90-90 goals.

This study is part of the PhD project of Anneleen Kiekens, titled “Transdisciplinary approach to identify actionable causes of HIV drug resistance and to bridge the gap between science and practice: the interplay between scientific knowledge and case study evidence from Tanzania, South Africa and Belgium”. The master thesis of Eva De Vis (r0468224) titled “Mapping depression and non-adherence to anti-HIV therapy to uncover common treatment targets” is part of the PhD project as well.

METHODS

Definition for CHW

In order to have a clear understanding of what a CHW is, we use the definition given by the WHO: ‘*community health workers should be members of the communities where they work, should be selected by the communities, should be answerable to the communities for their activities, should be supported by the health system but not necessarily a part of its organization, and have shorter training than professional workers*’ (Lehmann U, 2007)[4].

Surrogate markers for HIV therapy outcome

For the measurement of HIV therapy outcome, we used the proportion of patients with undetectable viral load (VL), increase in CD4 cell count and time to treatment failure as surrogate markers. VL and CD4 cell count give us an idea of the patients’ response to the HIV therapy, as the goal of the therapy is to reach and maintain VL suppression and to increase CD4 cell count. Treatment success was defined as reaching VL suppression in at least two consecutive measurements within six months of start of ART therapy, and as maintaining VL suppression during the study period; otherwise the patient was classified as having treatment failure, irrespective of CD4 count. For VL suppression we adopted the cut-offs as used by the included papers. The majority of the papers defined VL suppression as less than 400 copies per millilitre, while in some papers the cut-off was set on less than 200 copies, 500 copies or 1000 copies per millilitre. In absence of VL measurements, patients were usually classified as treatment experiencing success if the CD4 cell count increased above 200 cells per microliter of blood. In case of CD4 cell count follow-up above this threshold, a gradual increase until a healthy count is reached, is indicative for good treatment response[15]. CD4 count was not used to define treatment failure.

Standard of care (SOC)

SOC was equivalent amongst all studies. In SOC, patients were seen at the clinic by a nurse, and/or a clinical officer and/or a doctor. SOC consisted of health assessment, adherence assessment, HIV education and counselling and prescription of ART for one, two or three months. Patients then had to present to the pharmacy where ART was dispensed according to national guidelines, which were roughly similar in the various countries of the studies. In case the CHW intervention took place outside the clinic, patients had to visit the clinic less frequently than under SOC.

Search strategy and study selection

Between June 2018 and October 2018, we conducted a comprehensive literature search in PubMed, Web of Science and Embase. Inclusion criteria for our search were: studies had to be conducted in SSA, had to report biological HIV outcomes (viral load or CD4 cell count) and had to report on the contribution of CHWs, as described by the definition of the WHO, on HIV therapy outcome. Studies on children or on the co-pathology of HIV and tuberculosis were excluded. Ongoing trials without preliminary results were excluded. The full search strategy for each of the three databases is available in Addendum 1.

Data extraction and analysis

Data extraction from the literature was performed using a specific extraction format in Excel, including literature reference of the study, purpose, design, intervention under study and duration, tasks of CHWs during intervention, demographics of patients and the HIV therapy outcomes. A narrative summarizes the results of the primary analysis, in which we describe the impact of CHW interventions on biological HIV outcomes. For the secondary analysis on CHW tasks, we looked at the different tasks CHWs performed in each study. We studied the distribution and character of the tasks quantitatively and qualitatively. With the help of B-course[16], a program for classification and dependency Bayesian network modelling, we exploratively visualized the conditional probabilistic dependencies between a specific variable or combination of variables and successful CHW interventions. For the explorative analyses we defined a CHW intervention as successful if the CHW intervention led either to significantly better therapy outcome compared to SOC or to at least 90 percent of treated patients reaching viral suppression. The data set used for the Bayesian network modelling included as variables: success of the intervention, study duration and the tasks performed by the CHWs. An extended methodology on B-course and our data set can be found in Addendum 2. For the explorative dependency model, B-course predicted if connections were likely to be directed, mutual or undefined. We manually identified whether a connection between two variables as presented by B-course was likely to be positive, negative or undefined by plotting the two variables against each other in Excel. Since B-course could not depict this type of connection, we used Kumu[17] to reconstruct the dependency model with connection types. After obtaining both the explorative classification and dependency model, we compared the two models. A narrative summarizes the results of the secondary analysis.

RESULTS

Characteristics of included studies

The literature search resulted in 205 records, of which 26 papers were retained. After reading the full text of the papers, 8 studies were excluded. One study mentioned by an excluded systematic review was added since it met all inclusion criteria and had not shown up in our search. Figure 1 represents the flow chart of record and study selection.

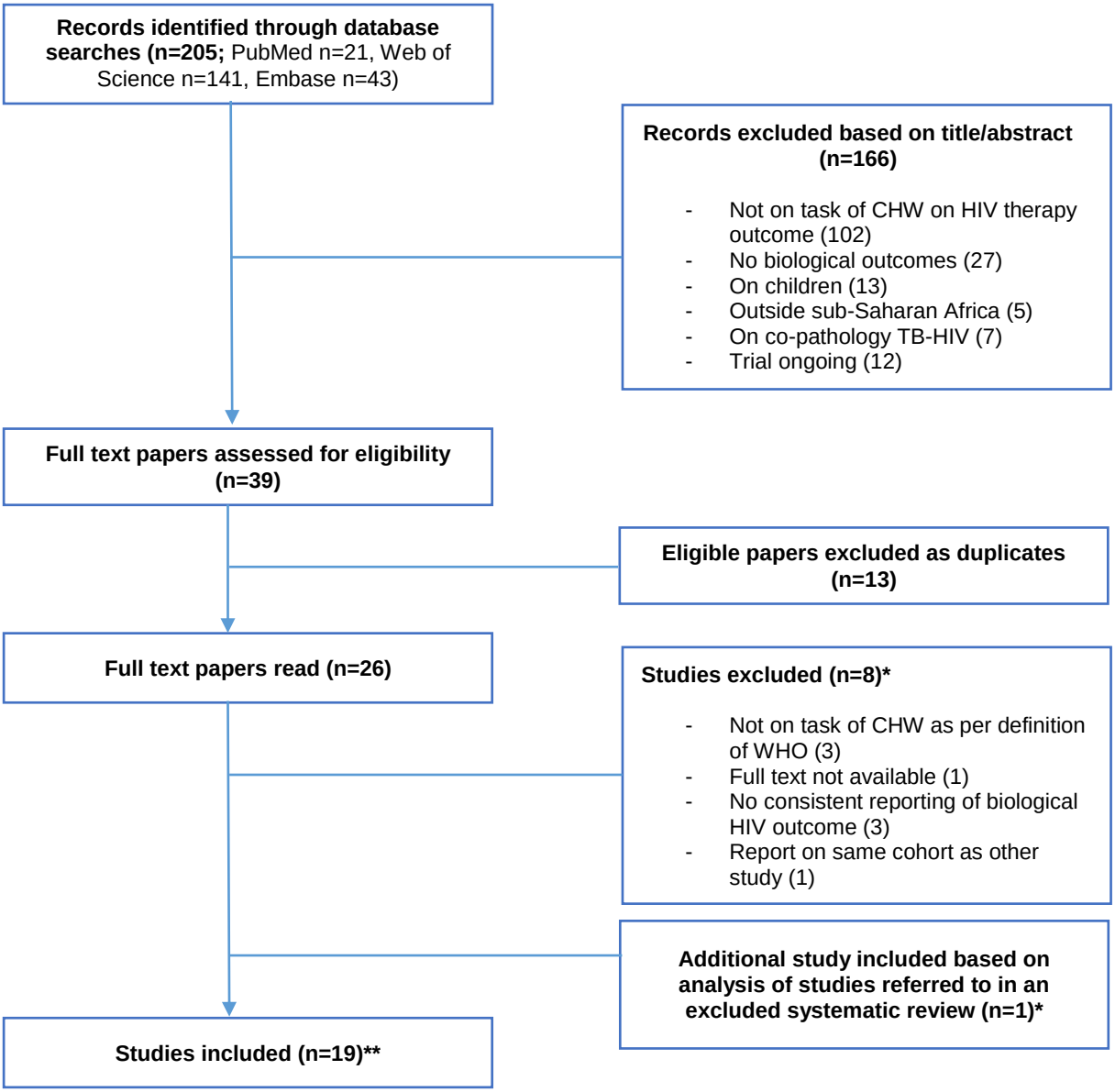

Figure 1 Flow chart of record and study selection
The number of records and the reasons for exclusion are depicted. For two papers, only part of the study population fulfilled the inclusion criteria. It is only this part of the study population that was included.
** cf. Addendum 3*
*** cf. Addendum 4*

More information on the excluded studies and on the inclusion of the additional study can be found in Addendum 3.

In total, we included 19 studies. Table III in Addendum 4 depicts the details of the included studies. Two of the papers discuss large studies for which only part of the population fulfilled the inclusion criteria[18,19], hence we only included the relevant part of the population. Statistical analysis was available for the included part of the population. Of the 19 studies, four were Randomised Controlled Trials (RCTs), eight were comparative cohort studies and seven studies evaluated a single arm intervention. All the studies were conducted in Eastern Africa or South Africa, except for one study from Burkina Faso. Most studies were performed over an extended period of time, with the shortest study having an intervention period of 3 months and the longest study running over 8 years. Sample sizes ranged from 129 up to 6194 HIV-positive study participants. In three studies, research was not carried out at the time of the intervention,

hence medical records were used for retrospective analysis. The total study population varied in terms of ART experience: nine studies reported findings on HIV-positive individuals initiating ART, four studies targeted HIV-patients on ART defined as stable, one study focused on HIV-patients with adherence problems and one study targeted both patients initiating ART and patients previously initiated. The remaining four studies recruited HIV-positive individuals enrolled in care, regardless of their therapy experience and adherence levels.

Effects on HIV therapy outcome

In all studies, the effects of CHW intervention on plasma VL suppression or CD4 cell count were not inferior to standard of care (SOC). This conclusion is based on data from studies that compared with a comparator arm and upon comparison with other studies in case of single arm interventions, as mentioned by the studies themselves, and as confirmed by an additional meta-analysis on efficacy of CHW programs[20].

Eight of the nineteen studies found statistically significant effects of CHW interventions on therapy outcome in comparison with SOC (indicated with * in Table 1, Figure 2 and Table III). Of these studies, one was a RCT and seven were comparative cohort studies. Three RCTs, of which one was not optimally designed to measure effects on biological outcome, and one comparative cohort study did not show statistically significant improvement in plasma VL or CD4 cell count. The remaining seven studies were single arm intervention studies, hence had no comparator-arm such that statistics could not be calculated.

Seven of the nineteen studies reported VL suppression in at least ninety percent of treated patients, hence reached the third target of the 90-90-90 goals (indicated with □ in Table 1, Figure 2 and Table III). Of these seven studies, three had a single arm intervention, three were comparative cohort studies and one was a RCT.

Distribution of CHW tasks

In the nineteen included studies, various tasks were given to the CHWs. The tasks of the CHWs as reported in the included studies are represented in Table 1. Figure 2 shows the number of times a CHW task was performed per study outcome.

Carrying out home visits was the most common task of the CHWs. The second most common task was giving adherence support to the individual. Four studies did not focus on the individual for adherence support but set up group adherence sessions instead[21–24]. One study provided both individual and group adherence support[25]. Other popular tasks were providing education and counselling and assessing the patients' health. Generally speaking, the more common tasks involved an important human support component, whereas less prevalent tasks had a more logistic character. Conducting home visits and providing adherence support, social or emotional support, education and counselling are all tasks that require a certain amount of human interaction, time and engagement from the care-provider. These tasks often help to improve the patients' well-being and self-efficacy. In all studies, CHWs covered at least one of these tasks. The more logistic tasks were often regarded as side-tasks in studies where CHWs had a broad range of duties.

Table 1 Tasks of the CHWs as reported in the included studies

Tasks of CHWs	*Number of studies in which CHWs fulfilled the task (N=19)*	Studies with significant results (N=8)*	Single arm studies with ≥90% of patients reaching VL suppression (N=4)□	Other studies (N=7)
Home visits	*15*	Achieng *(1/m)* Chang(2010)□ *(8/m)* Fatti *(4/m first month, then 1/m, quarterly when stable)* Franke *(30/m)* Igumbor *(as needed)* Kipp□ *(4/m)* Wouters *(4/m)*	Rich *(30/m)* Weidle *(4/m)*	Barnabas(2016) *(3/y)* Barnabas(2014) *(5/y)* Chang(2009) *(as needed)* Konate *(2 weekly visits, then 1/m)* Selke *(1/m)* van Rooyen *(3/y)*
Adherence support individual	*11*	Achieng, Chang(2010)□, Franke, Fatti, Igumbor, Kipp□, Wouters	Rich, Weidle	Chang(2009), Konate
HIV education + counselling	*10*	Chang(2010)□, Igumbor, Wouters	Grimsrud, Myer, Rich, Weidle	Barnabas(2016), Barnabas(2014), Konate
Health assessment	*9*	Achieng, Chang(2010)□, Franke, Kipp□	Grimsrud, Myer, Rich	Chang(2009), Selke
Adherence support group	*5*	Achieng, Bango□	Grimsrud, Myer	Peltzer
ART delivery	*5*	Bango□, Kipp□	Grimsrud, Myer	Selke
Social and/or emotional support	*4*	Franke, Wouters	Rich	Chang(2009)
Referral to care	*4*	Achieng, Chang(2010)□, Fatti		Barnabas(2014)
HIV testing and counselling (HTC)	*3*			Barnabas(2016), Barnabas(2014), van Rooyen
Adherence assessment	*3*	Chang(2010)□		Chang(2009), Selke
Directly observed therapy (DOT)	*2*	Franke	Rich	
Food provision	*2*	Franke	Rich	
Transportation stipends for clinic visit	*2*	Franke	Rich	
Facilitation of clinic visit	*2*	Franke		Barnabas(2016)
Condom distribution	*1*			Konate

□*VL suppression ≥90% of patients was reached in 7 studies in total, of which 3 studies yielded significant results. Hence, these 3 studies are displayed in the column titled 'Studies with significant results'.*
Abbreviations: ART = antiretroviral therapy; m = month; y = year

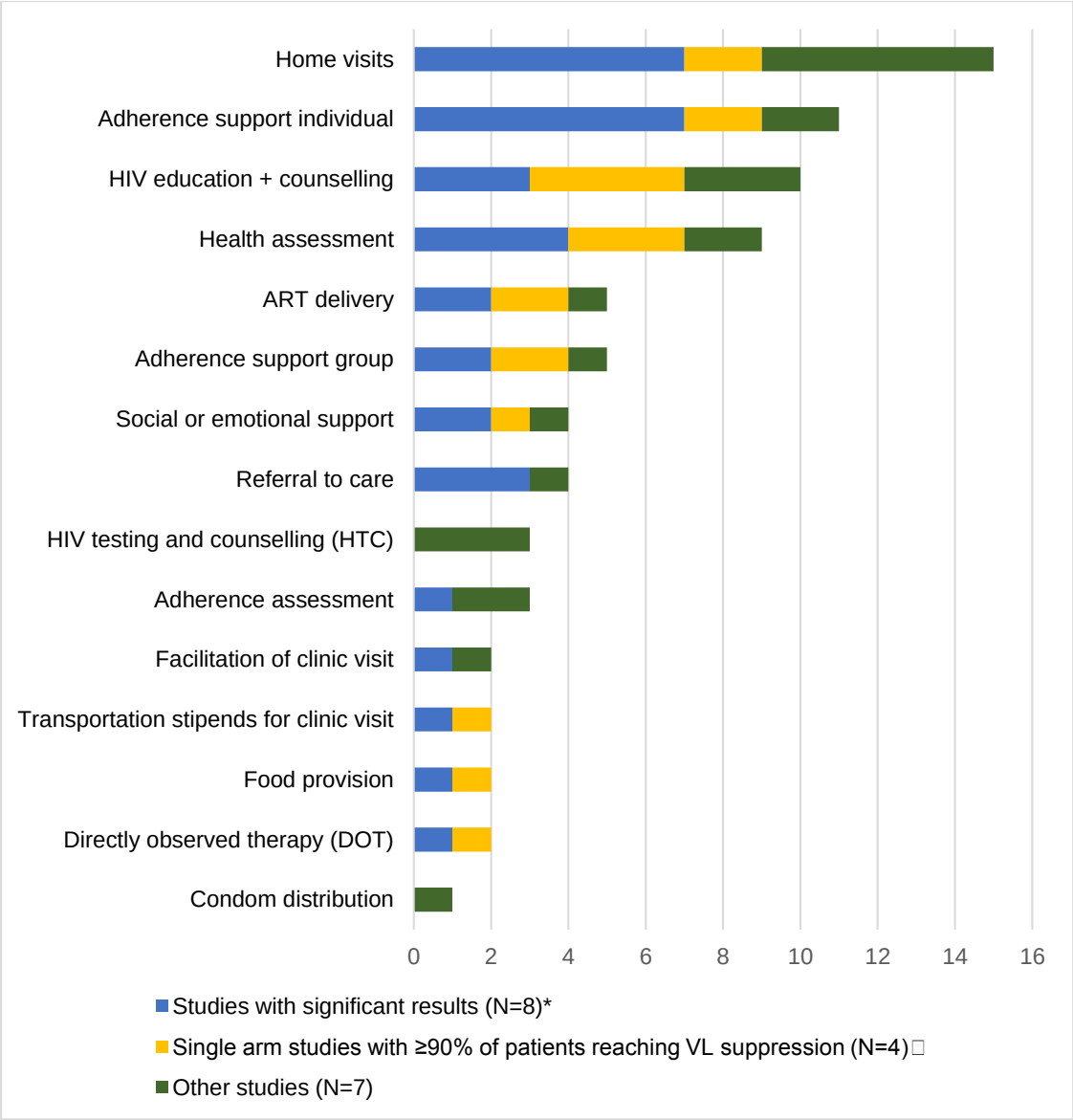

Figure 2 Number of times a CHW task was performed per study outcome
□Viral load suppression in ≥90% of patients was reached in 7 studies in total, of which three studies yielded significant results. Hence, these three studies are displayed in the category titled 'Studies with significant results'.
Abbreviations: ART = antiretroviral therapy

Whereas home visits were conducted in the majority of studies, there was a substantial variability in frequency of home visits. In studies that reported significant results or in studies with at least 90 percent of patients attaining VL suppression, CHWs visited the patients' home at least once a month, with a maximum visiting frequency of once a day. In the other studies, CHWs did not conduct as many home visits (cf. Table 1).

Many studies assigned a multitude of tasks to the CHWs. The median number of tasks was four. There was one study in which CHWs solely had to organize the adherence support group[26]. In two studies the CHWs had as many as 7[27] or 8[28] tasks. The number of tasks assigned to CHWs did not impact HIV therapy outcome.

Explorative analyses of CHW interventions

For the secondary analysis on CHW tasks, we performed explorative classification and dependency Bayesian network analyses. Since we did not have access to individual patient data, the unit included in the Bayesian network analyses was the study itself, such that connections represent differences between studies, not between patients. As mentioned in methods, we defined a CHW intervention study as successful if the CHW intervention led either to significantly better therapy outcome compared to SOC or to at least 90 percent of treated patients reaching viral suppression. Given the small number of included studies and the multitude of tasks assigned to CHWs in some studies, study design is a confounding factor in the interpretation of the results. This will be illustrated with an example below.

The purpose of the explorative dependency network analysis was to uncover potential combinations of variables linked to successful CHW interventions and their dependencies. After predicting the connection types (positive, negative, undefined; directed, mutual, undefined), we reconstructed the explorative dependency model (Figure 3 and Figure 4). The original explorative dependency model provided by B-course can be found in Addendum 5.

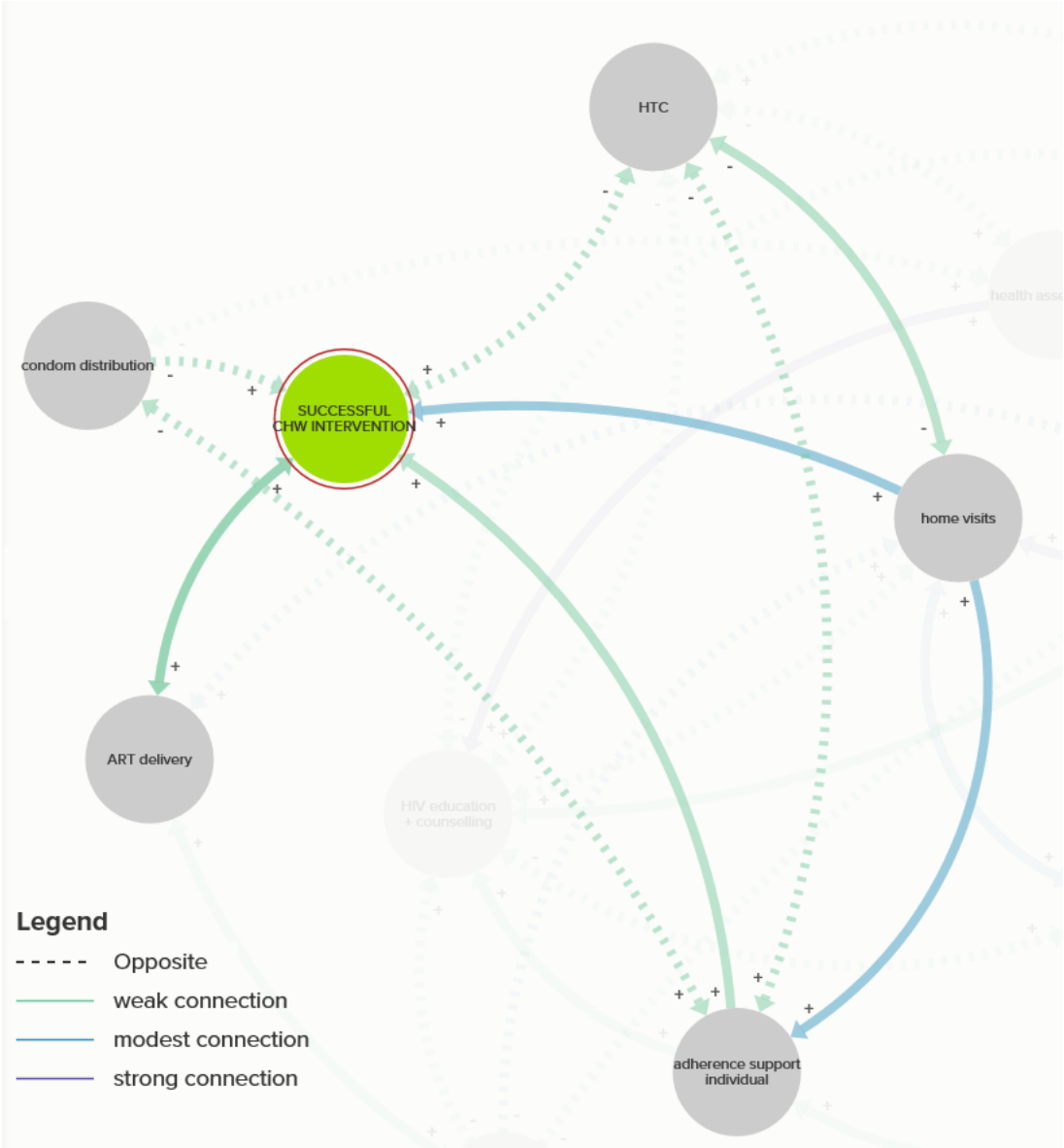

Figure 3 Explorative dependency model centred around 'successful CHW interventions'
The colours of the arcs represent the probable strength of the dependencies as indicated in the legend. The arrows indicate whether a connection is likely to be directed or mutual. The absence of arrows means that the direction of the connection could not be predicted. + and – represent the probable effect of the variables on each otter. Dotted arcs represent opposite effects (+ - or - +). When no + or – is given, the dependency could not be predicted.
Abbreviations: ART = antiretroviral therapy; HTC = HIV testing and counselling

Variables directly linked with 'successful CHW intervention' were 'adherence support individual', 'HIV testing and counselling (HTC)', 'ART delivery', 'condom distribution' and 'home visits'. The types of the connections varied. The connection between 'successful CHW intervention' and 'adherence support individual' was directed and positive, hence having CHWs provide individual adherence support was predictive of a successful CHW intervention. The connection between 'successful CHW intervention and 'HTC' was mutual and opposite, hence having a successful CHW intervention predicted that HTC was not provided AND not providing HTC predicted having a successful CHW intervention. The connection between success and ART delivery was mutual and positive. The connection between success and condom distribution was directed and opposite. Conducting home visits was linked with success in a 1-directional and positive way.

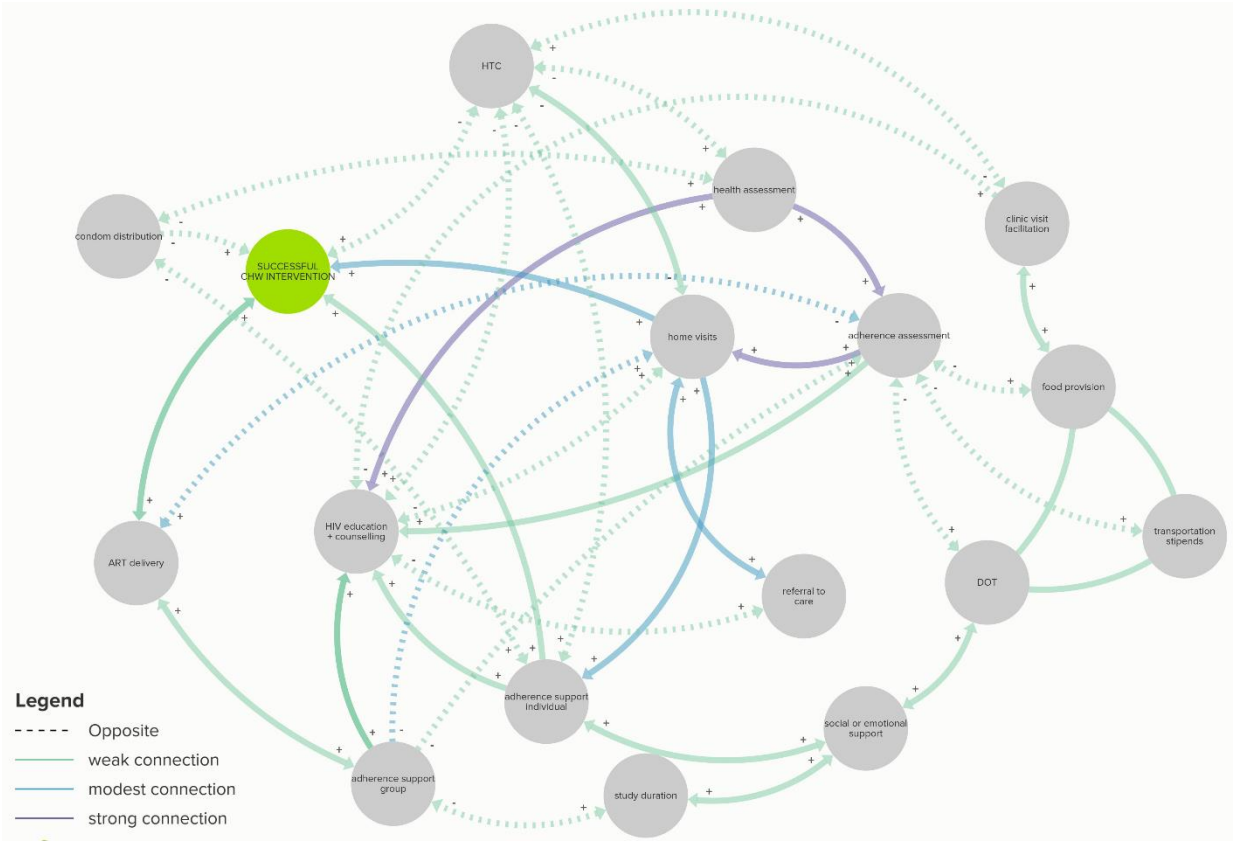

Figure 4 Explorative dependency model
The colours of the arcs represent the probable strength of the dependencies as indicated in the legend. The arrows indicate whether a connection is likely to be directed or mutual. The absence of arrows means that the direction of the connection could not be predicted. + and – represent the probable effect of the variables on each otter. Dotted arcs represent opposite effects (+ - or - +). When no + or – is given, the dependency could not be predicted.
Abbreviations: ART = antiretroviral therapy; HTC = HIV testing and counselling; DOT = directly observed therapy

In the explorative dependency network, the strongest dependencies were found between ‘adherence assessment’ and ‘home visits’, between ‘health assessment’ and ‘adherence assessment’ and between ‘health assessment’ and ‘HIV education + counselling’. These three connections were directed and had a positive effect. If any of these connections would be removed, this would result in a model with a probability of less than one millionth of that of the original model.

Modest dependencies were found between ‘home visits’ and ‘successful CHW intervention’ (directed and positive), between ‘home visits’ and ‘adherence support individual’ (directed and positive), between ‘adherence support group’ and ‘home visits’ (directed and opposite), between ‘ART delivery’ and ‘adherence assessment’ (mutual and opposite) and between ‘referral to care’ and ‘home visits’ (mutual and positive). If any of these connections would be removed, this would result in a model with a probability of less than one thousandth of that of the original model.

When looking more closely at the explorative dependency model, we see that the variable ‘home visits’ has seven connections, of which five are modest or strong. This ratio is higher than for other variables. The variables ‘health assessment’ and ‘adherence assessment’ have a relatively high ratio of stronger connections as well. Having a stronger connection between variables means that these two variables often appeared together in the same studies. The variables ‘HIV education + counselling’ and ‘adherence assessment’ both have eight connections, which is the highest number of connections on the map.

With the explorative classification network analysis, we aimed to investigate which variables were likely to be the strongest predictors of success of a CHW intervention. B-course indicated the variables (1) ‘adherence support individual’, (2) ‘HTC’, (3) ‘ART delivery, (4) ‘adherence assessment’, (5) ‘referral to care’, (6) ‘directly observed therapy (DOT)’ and (7) ‘condom distribution’ as the best subset for predicting success of the CHW intervention. If predictor (1 or 2), (3 or 4), (5 or 6 or 7) would be removed, the predictive accuracy of the model would go down by 17.86%, 10.71% or 3.57% respectively.

We used the knowledge from the explorative dependency model and predicted the connection types in order to interpret the predicting subset of the explorative classification model. This resulted in the following findings: (1) providing adherence support of the individual predicted success of the CHW intervention, (2) not providing HTC predicted success of the CHW intervention and vice versa, (3) delivering ART predicted success of the CHW intervention and vice versa, (4) not conducting adherence assessment predicted success of the CHW intervention, (5) conducting DOT predicted success of the CHW, (6) referring to care predicted success of the CHW intervention and (7) not distributing condoms predicted success of the CHW intervention.

Upon comparing the explorative dependency model with the explorative classification model, we found that all the variables directly linked with ‘successful CHW intervention’ in the explorative dependency model, with exception of ‘home visits’, were listed in the predictive subset of the explorative classification model. Conversely, ‘adherence assessment’, ‘referral to care’ and ‘DOT’ were indicated as predictors, however, they were not directly linked with ‘successful CHW intervention’ in the explorative dependency model. This means that their predictive effect is indirect through (an)other variable(s).

The models generated above have important limitations. Given the small number of included studies and the multitude of tasks assigned to CHWs in some studies, the results need to be interpreted with care. As an example, 'condom distribution' has been designated as a negative predictor for 'successful CHW intervention' in the explorative classification model. However, this connection is based on one study only. In this study, condom distribution was one of the tasks and the study outcome was not successful[18].

Further, study design could also be a confounding factor in the interpretation of the results. For example, there were four studies that focussed on stable patients. Three of the four studies organised adherence group sessions with ART delivery. One of these three studies showed significant effects of the CHW intervention[21], whereas the other two studies maintained VL suppression in at least 90 percent of patients, without showing significance[22,23]. According to our definition of success, we could classify these studies as successful CHW intervention studies. In the explorative dependency model however, we do not see a direct connection between 'adherence support group' and 'successful CHW intervention'. The connection is indirect, via 'ART delivery'. This is because 'adherence support group' was more frequently linked with other variables than ART delivery, hence the best way of linking 'adherence support group' to 'successful CHW intervention', with as little connections as possible, was via 'ART delivery'. Further, of these three studies, both health assessment and HIV education + counselling were performed in two studies. However, we cannot see a link between 'adherence support group' and 'health assessment'. Hence, a direct connection between two variables can be absent or present because of study design, not necessarily because of (lack of) effect. If a connection is present, but its presence cannot be attributed to study design, we can assume that the connection shows a certain effect. When we look at the variable 'successful CHW intervention', the variables 'ART delivery', 'adherence support individual' and 'home visits' seem to be positively connected independently of study design, hence we assume that these tasks are predictive for success.

Given the described limitations, the interpretation of the results is difficult, and we chose not to withhold a certain task or a particular combination of tasks as strong predictors of a successful CHW intervention.

DISCUSSION

Over the past decennia, CHWs emerged as the much-needed answer to the health force shortages in developing countries. The positive impact of CHW programs on ART outcome in SSA is widely assumed, however, little high-quality evidence on large-scale CHW interventions is available[4,8–12]. Furthermore, there are diverging views on what a CHW is and which specific tasks CHWs need to fulfil in order to conduct successful CHW interventions.

This literature review confirms that CHW interventions are not inferior to SOC, they can improve patient treatment outcomes, and they can contribute to reaching 90 percent of treated patients being virally suppressed, which is the third goal of the 90-90-90 goals. This confirms the WHO's assertion that community level interventions for people living with HIV are feasible and must be supported[13,14]. As such, CHWs can contribute to relieving the high work load for health care workers. The main tasks of CHWs involved an important human support component, with conducting home visits as the most common CHW task. We found indications that ART delivery, individual adherence support and frequent home visits were predictive of a

successful CHW intervention, defined as improved therapy outcome compared to SOC or reaching 90 percent of treated patients being virally suppressed. However, given the difficulty in interpretation of the analyses, we chose not to withhold a certain task or a particular combination of tasks as strong predictors of a successful CHW intervention.

Given the strict inclusion criteria, we reached a limited number of included studies. Although we searched for studies covering all of SSA, we found mainly studies of Eastern and Southern Africa. Of the included studies, there was a substantial number of single arm intervention studies and few were RCTs. Three of the four included RCTs did not show statistically significant effects of CHW intervention on HIV therapy outcome. In one RCT[29] this was likely due to a design that was not optimally suited to measure effects on biological therapy outcome, in combination with limited ART supply at the clinics. The other RCT[26] ran over a very short period of time (3 months), in which the CHWs gave three educational sessions. Given that the study focused on patients with adherence problems, and that there was limited contact time for adherence support, the intervention might not have been comprehensive enough to show effects. The third RCT[24] gathered fewer patients than they originally aimed for and was likely underpowered. Being clinically stable on ART for a minimum of 3 months with no adherence issues was an inclusion criterium for this study. Despite being defined as stable by the study, the percentage of virally suppressed patients did not reach 90 percent.

For the measurement of HIV therapy outcome, we used VL and CD4 cell count as surrogate markers. As for the VL outcome, we accepted the cut-off values as used in the different studies. Although the cut-off values differ amongst the studies, this did probably not influence the trends observed. The fact that we used biological treatment outcome might affect our ability to assess a beneficial effect of CHWs, since the most immediate effect of their intervention is considered to be improved linkage to care, which is anticipated to result in improved adherence and improved biological outcome of treatment. As such, we might have excluded studies that only measured linkage to care or a measurement of adherence that did not involve biological outcomes. Our choice was guided by our goal to understand CHW interventions in the context of therapy outcome and HIV drug resistance, which is best measured with biological variables.

Regarding the tasks of the CHWs and the Bayesian network analyses, we encountered some difficulties. Given the small number of included studies and the multitude of tasks assigned to CHWs in some studies, study design became a confounding factor. Hence, the interpretation of the results is difficult. Further, it was unclear to what extent the task ‘HIV education and counselling’ overlapped with home visits and adherence counselling. The same applies to the task ‘emotional or social support’. It might also be that the beneficial effect of specific tasks is context specific, but we had no data to address this.

As for future research, we deem it important that high-quality studies focus on which of the CHWs’ tasks are most effective in terms of treatment outcome for a particular patient population, and to explore whether some of the beneficial effects are context dependent. In case other studies confirm our hypothesis that delivering ART, providing individual adherence support and conducting frequent home visits are predictive of a successful CHW intervention, this can direct future CHW interventions. The required frequency of home visits must also be studied. As cost-effectiveness is important for health system interventions, we need to know what a high enough frequency of visits is, and how de-escalation of visits over the long-term impacts HIV therapy outcome.

CONCLUSIONS

We found that CHWs interventions are not inferior to SOC and might even be beneficial, which is in line with the assertion that CHW interventions can help to improve HIV patient care and relieve the burden on the health care system. Despite the limitations of the analyses on the CHW tasks, we found indications that ART delivery, individual adherence support and frequent home visits were predictive of a successful CHW intervention. Further research is needed to be able to judge whether any single task or particular combination of tasks is significantly correlated with success of a CHW intervention.

CONFLICT OF INTEREST

None

FINANCIAL DISCLOSURE

None

FUNDING

none

ACKNOWLEDGEMENT

I would like to thank several people for their contributions, directly or indirectly, to this master thesis.

In the first place I would like to express my gratitude to my promotor Prof Dr Anne-Mieke Vandamme and my mentor Anneleen Kiekens. They guided me throughout the process and gave critical input when needed. I would like to stress that I strongly appreciate their efforts, especially towards the finalization of the master thesis.

Second, I would like to thank Kristof Theys from the Rega Institute for his help with the Bayesian network modelling. He gave me insight in this particular approach of modelling and guided me through the analyses.

Next, I cannot express how grateful I am that I had the chance to participate in the Transdisciplinary Insights Honours program. The coaches and stakeholders of the HIV drug resistance challenge piqued my interest in the HIV epidemics and were very eager to share their experience and insights.

I would also like to show appreciation to the students and health care staff I worked with in Uganda in the summer of 2017 and 2018, in the context of the Northern Uganda Village Health Outreach Program (NUV-HOP). With NUV-HOP, I got the opportunity to get a thorough understanding of the health situation in Uganda. My special thanks go to the staff of the ART clinic of Gulu Regional Referral Hospital, for welcoming me with open arms and for answering all my questions.

Further, I would like to thank the research staff at the Centre for the Aids Program of Research in South Africa (CAPRISA). I thank Prof Ayesha BM Kharsany, Dr. Leila E Mansoor, Dr. Pamela P Gumbi and Santhana Gengiah in particular, for sharing their knowledge with me and for giving me insight in the current HIV epidemics in South Africa.

Finally, I am very grateful for the support of my friends and family throughout my study.

BIBLIOGRAPHY

1. UNAIDS. *UNAIDS Data 2017*. (2017). doi:978-92-9173-945-5
2. World Health Organization. *Working together for health: The World Health Report 2006*. (2006).
3. Organization, W. H. Density of physicians (total number per 1000 population, latest available year). *WHO* (2018). Available at: http://www.who.int/gho/health_workforce/physicians_density/en/. (Accessed: 21st August 2018)
4. Lehmann, U. & Sanders, D. *Community health workers: What do we know about them? The state of the evidence on programmes, activities, costs and impact on health outcomes of using community health workers*. *World Health Organization* (2007). doi:10.1097/JAC.0000000000000086
5. Giblin, P. T. Effective utilization and evaluation of indigenous health care workers. *Public Health Rep.* **104,** 361–8 (1974).
6. Maes, K. & Kalofonos, I. Becoming and remaining community health workers: Perspectives from Ethiopia and Mozambique. *Soc. Sci. Med.* **87,** 52–59 (2013).
7. World Health Organization. *National experience in the use of community health workers: a review of current issues and problems*. (1983).
8. Wouters, E., Van Damme, W., van Rensburg, D., Masquillier, C. & Meulemans, H. Impact of community-based support services on antiretroviral treatment programme delivery and outcomes in resource-limited countries: a synthetic review. *BMC Health Serv. Res.* **12,** 1–17 (2012).
9. Kanters, S. *et al.* Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV* **4,** e31–e40 (2017).
10. Haberer, J. E. *et al.* Improving antiretroviral therapy adherence in resource-limited settings at scale: a discussion of interventions and recommendations. *J. Int. AIDS Soc.* **20,** 21371 (2017).
11. Franke, M. F. *et al.* Improved Retention Associated With Community-Based Accompaniment for Antiretroviral Therapy Delivery in Rural Rwanda. *Clin. Infect. Dis.* **56,** 1319–1326 (2013).
12. Wouters, E., Van Damme, W., Van Loon, F., Van Rensburg, D. & Meulemans, H. Public-sector ART in the Free State Province, South Africa: Community support as an important determinant of outcome. *Soc. Sci. Med.* **69,** 1177–1185 (2009).
13. World Health Organization. *Global action plan for HIV drug resistance 2017-2021*. *WHO Geneva* (2016).
14. World Health Organization. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*. *World Health Organization* (2016). doi:10.1016/j.jped.2014.04.007
15. HIV & AIDS Information: CD4 cell counts. *NAM Publications* (2019). Available at: http://www.aidsmap.com/CD4-cell-counts/page/1327484/. (Accessed: 26th January 2019)
16. B-Course. Available at: http://b-course.hiit.fi/obc/. (Accessed: 27th January 2019)
17. Kumu. Available at: https://kumu.io/. (Accessed: 30th January 2019)
18. Konate, I. *et al.* Linking HIV prevention and care for community interventions among high-risk women in Burkina Faso - the ARNS 1222 'Yerelon' cohort. (Implementation and Operational Research in Francophone Africa.). *J. Acquir. Immune Defic. Syndr.* **57,** S50–S54 (2011).
19. van Rooyen, H. *et al.* High HIV testing uptake and linkage to care in a novel program of home-based HIV counseling and testing with facilitated referral in KwaZulu-Natal, South Africa. *J Acquir Immune Defic Syndr* **64,** e1–e8 (2013).
20. Ivers, L. C., Kendrick, D. & Doucette, K. Efficacy of Antiretroviral Therapy Programs in Resource- Poor Settings: A Meta- analysis of the Published Literature. *Clin. Infect. Dis.* **41,** 217–224 (2005).
21. Bango, F., Ashmore, J., Wilkinson, L., van Cutsem, G. & Cleary, S. Adherence clubs

for long-term provision of antiretroviral therapy: cost-effectiveness and access analysis from Khayelitsha, South Africa. *Trop. Med. Int. Heal.* **21,** 1115–1123 (2016).
22. Grimsrud, A., Sharp, J., Kalombo, C., Bekker, L.-G. & Myer, L. Implementation of community-based adherence clubs for stable antiretroviral therapy patients in Cape Town, South Africa. *J. Int. AIDS Soc.* **18,** 19984 (2015).
23. Myer, L. *et al.* Differentiated models of care for postpartum women on antiretroviral therapy in Cape Town, South Africa: A cohort study. *J. Int. AIDS Soc.* **20,** 32–40 (2017).
24. Selke, H. M. *et al.* Task-Shifting of Antiretroviral Delivery From Health Care Workers to Persons Living With HIV / AIDS : Clinical Outcomes of a Community-Based Program in Kenya. *J Acquir Immune Defic Syndr* **55,** 483–490 (2010).
25. Achieng, L. *et al.* An Observational Cohort Comparison of Facilitators of Retention in Care and Adherence to Anti-Eetroviral Therapy at an HIV Treatment Center in Kenya. *PLoS One* **7,** e32727 (2012).
26. Peltzer, K. *et al.* Efficacy of a lay health worker led group antiretroviral medication adherence training among non-adherent HIV-positive patients in KwaZulu-Natal, South Africa: Results from a randomized trial. *SAHARA-J J. Soc. Asp. HIV/AIDS* **9,** 218–226 (2012).
27. Rich, M. L. *et al.* Excellent Clinical Outcomes and High Retention in Care Among Adults in a Community-Based HIV Treatment Program in Rural Rwanda. *J Acquir Immune Defic Syndr* **59,** 35–42 (2012).
28. Franke, M. F. *et al.* Improved Retention Associated With Community-Based Accompaniment for Antiretroviral Therapy Delivery in Rural Rwanda. *Clin. Infect. Dis.* **56,** 1319–1326 (2013).
29. Barnabas, R. V. *et al.* Uptake of antiretroviral therapy and male circumcision after community-based HIV testing and strategies for linkage to care versus standard clinic referral: A multisite, open-label, randomised controlled trial in South Africa and Uganda. *Lancet HIV* **3,** e212–e220 (2016).
30. Igumbor, J. O., Scheepers, E., Ebrahim, R., Jason, A. & Grimwood, A. An evaluation of the impact of a community-based adherence support programme on ART outcomes in selected government HIV treatment sites in South Africa. *AIDS Care* **23,** 231–236 (2011).
31. Chang, L. W. *et al.* Two year virologic outcomes of an alternative AIDS care model: evaulation of a peer health worker and nurse-staffed community-based program in Uganda. *J Acquir Immune Defic Syndr* **50,** 276–282 (2009).
32. Assefa, Y. *et al.* Effectiveness and acceptability of delivery of antiretroviral treatment in health centres by health officers and nurses in Ethiopia. *J. Heal. Serv. Res. Policy* **17,** 24–29 (2012).
33. Francis, J. *et al.* The impact of community delivery of antiretroviral therapy on viral load suppression: Findings from a pragmatic randomized non-inferiority trial in Dar es Salaam, Tanzania. *J. Int. AIDS Soc.* **21,** e25148 (2018).
34. Johnston, V. *et al.* Second-line antiretroviral therapy in a workplace and community-based treatment programme in South Africa: Determinants of virological outcome. *PLoS One* **7,** (2012).
35. Mdege, N. D., Chindove, S. & Ali, S. The effectiveness and cost implications of task-shifting in the delivery of antiretroviral therapy to HIV-infected patients: A systematic review. *Health Policy Plan.* **28,** 223–236 (2013).
36. Nachega, J. B. *et al.* Randomized Controlled Trial of Trianed Patient-Nominated Treatment Supporters Providing Partial Directly Observed Antiretroviral Therapy. *AIDS* **24,** 1273–1280 (2010).
37. Robbins, R. N. *et al.* Enhancing Lay Counselor Capacity to Improve Patient Outcomes with Multimedia Technology. *AIDS Behav.* **19,** 163–176 (2015).
38. Vogt, F. *et al.* Tracing defaulters in HIV prevention of mother-to-child transmission programmes through community health workers: Results from a rural setting in Zimbabwe. *J. Int. AIDS Soc.* **18,** 1–10 (2015).

39. Wouters, E., van Damme, W., van Rensburg, D. & Meule. Impact of baseline health and community support on antiretroviral treatment outcomes in HIV patients in South Africa. *AIDS* **22,** 2545–2548 (2008).
40. Chang, L. W. *et al.* Effect of peer health workers on AIDS care in Rakai, Uganda: a cluster-randomized trial. *PLoS One* **5,** e10923 (2010).
41. Barnabas, R. V *et al.* Initiation of antiretroviral therapy and viral suppression after home HIV testing and counselling in KwaZulu-Natal, South Africa, and Mbarara dsitrict, uganda: a prospective, observational intervention study. *Lancet HIV* **1,** 68–76 (2014).
42. Fatti, G., Mothibi, E., Shaikh, N. & Grimwood, A. Improved long-term antiretroviral treatment outcomes amongst patients receiving community-based adherence support in South Africa. *AIDS Care* **28,** 1365–1372 (2016).
43. Kipp, W. *et al.* Antiretroviral treatment for HIV in rural Uganda: Two-year treatment outcomes of a prospective health centre/community-based and hospital-based cohort. *PLoS One* **7,** 1–9 (2012).
44. Weidle, P. J. *et al.* Adherence to antiretroviral therapy in a home-based AIDS care programme in rural Uganda. *Lancet* **368,** 1587–1594 (2006).

ADDENDUM 1: SEARCH STRATEGIES

PubMed

Search ((((((((((community health aides[MeSH Terms]) OR community health aide[MeSH Terms]) OR village health worker[MeSH Terms]) OR village health workers[MeSH Terms]) OR barefoot doctor[MeSH Terms]) OR barefoot doctors[MeSH Terms]) OR "community health workers"[MeSH Terms])) OR "community health workers"[Text Word])) AND ((((("HIV"[Mesh]) OR "Acquired Immunodeficiency Syndrome"[Mesh]) OR HIV[Text Word]))) AND (("Africa South of the Sahara"[Mesh]) OR ((Botswana OR Burundi OR Ethiopia OR Zimbabwe OR Mozambique OR Malawi OR Zambia OR Tanzania OR Kenya OR Uganda OR Rwanda OR Senegal OR gambia OR guinea OR sierra leone OR Liberia OR cote d-ivoire OR Burkina faso OR Ghana OR togo OR benin OR niger OR Nigeria OR Cameroon OR gabon OR congo OR angola OR Namibia OR Lesotho OR Swaziland OR Somalia OR Djibouti OR Eritrea OR sudan OR "south* africa" OR "sub-saharan Africa" OR "east africa" OR "west africa" OR "central africa")))) AND (((((("viral load"[MeSH Major Topic]) OR "cd4 lymphocyte count"[MeSH Terms])) OR "viral load"[Text Word]) OR "CD4 cell count"[Text Word])

Embase

(('health aides' OR 'community health aides'/exp OR 'community health aides' OR 'community health workers'/exp OR 'community health workers' OR 'lay health workers'/exp OR 'lay health workers') AND or, AND 'health volunteers' OR 'health communicators' OR 'adherence supporters' OR 'health guides' OR 'health visitors' OR 'adherence workers' OR 'lay counsellors' OR 'health aide' OR 'community health aide' OR 'community health worker'/exp OR 'community health worker' OR 'lay health worker'/exp OR 'lay health worker' OR 'health volunteer' OR 'health communicator' OR 'adherence supporter' OR 'health guide' OR 'health visitor'/exp OR 'health visitor' OR 'adherence worker' OR 'lay counsellor') AND ('hiv' OR 'hiv'/exp OR hiv OR 'aids' OR 'aids'/exp OR aids OR 'acquired immune deficiency syndrome'/exp OR 'acquired immune deficiency syndrome' OR 'acquired immunodeficiency syndrome'/exp OR 'acquired immunodeficiency syndrome' OR 'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus') AND ('viral load'/exp OR 'viral load' OR 'viral burden'/exp OR 'viral burden' OR 'viral titer'/exp OR 'viral titer' OR 'virus titer'/exp OR 'virus titer' OR 'cd4 cell count'/exp OR 'cd4 cell count' OR 'cd4 lymphocyte count'/exp OR 'cd4 lymphocyte count' OR 'cd4+ count'/exp OR 'cd4+ count' OR 'cd4 count'/exp OR 'cd4 count' OR 't4 lymphocyte count' OR 'cd4+ cell count'/exp OR 'cd4+ cell count' OR 'cd4 cell counts'/exp OR 'cd4 cell counts' OR 'cd4 lymphocyte counts'/exp OR 'cd4 lymphocyte counts' OR 'cd4+ counts'/exp OR 'cd4+ counts' OR 'cd4 counts'/exp OR 'cd4 counts' OR 't4 lymphocyte counts' OR 'cd4+ cell counts'/exp OR 'cd4+ cell counts') AND (((((('africa south of the sahara'/exp OR 'africa south of the sahara' OR 'botswana' OR 'botswana'/exp OR botswana OR 'burundi' OR 'burundi'/exp OR burundi OR 'ethiopia' OR 'ethiopia'/exp OR ethiopia OR 'zimbabwe' OR 'zimbabwe'/exp OR zimbabwe OR 'mozambique' OR 'mozambique'/exp OR mozambique OR 'malawi' OR 'malawi'/exp OR malawi OR 'zambia'/exp OR 'zambia' OR zambiaor) AND ('tanzania'/exp OR 'tanzania') OR 'tanzania'/exp OR tanzania OR 'kenya' OR 'kenya'/exp OR kenya OR 'uganda' OR 'uganda'/exp OR uganda OR 'rwanda' OR 'rwanda'/exp OR rwanda OR 'senegal' OR 'senegal'/exp OR senegal OR 'gambia' OR 'gambia'/exp OR gambia OR 'guinea' OR 'guinea'/exp OR guinea OR sierra) AND leone OR 'liberia' OR 'liberia'/exp OR liberia OR cote) AND 'd ivoire' OR burkina) AND faso OR 'ghana' OR 'ghana'/exp OR ghana OR 'togo' OR 'togo'/exp OR togo OR 'benin' OR 'benin'/exp OR benin OR 'niger' OR 'niger'/exp OR niger OR 'nigeria' OR 'nigeria'/exp OR nigeria OR 'cameroon' OR 'cameroon'/exp OR cameroon OR 'gabon' OR 'gabon'/exp OR gabon OR 'congo' OR 'congo'/exp OR congo OR 'angola' OR

'angola'/exp OR angola OR 'namibia' OR 'namibia'/exp OR namibia OR 'lesotho' OR 'lesotho'/exp OR lesotho OR 'swaziland' OR 'swaziland'/exp OR swaziland OR 'somalia' OR 'somalia'/exp OR somalia OR 'djibouti' OR 'djibouti'/exp OR djibouti OR 'eritrea' OR 'eritrea'/exp OR eritrea OR 'sudan' OR 'sudan'/exp OR sudan OR 'south* africa' OR 'sub-saharan africa'/exp OR 'sub-saharan africa' OR 'east africa'/exp OR 'east africa' OR 'west africa'/exp OR 'west africa' OR 'central africa'/exp OR 'central africa')

Web of Science

TS=((('health aides' OR 'community health aides'/exp OR 'community health aides' OR 'community health workers'/exp OR 'community health workers' OR 'lay health workers'/exp OR 'lay health workers') AND or, AND 'health volunteers' OR 'health communicators' OR 'adherence supporters' OR 'health guides' OR 'health visitors' OR 'adherence workers' OR 'lay counsellors' OR 'health aide' OR 'community health aide' OR 'community health worker'/exp OR 'community health worker' OR 'lay health worker'/exp OR 'lay health worker' OR 'health volunteer' OR 'health communicator' OR 'adherence supporter' OR 'health guide' OR 'health visitor'/exp OR 'health visitor' OR 'adherence worker' OR 'lay counsellor') AND ('hiv' OR 'hiv'/exp OR hiv OR 'aids' OR 'aids'/exp OR aids OR 'acquired immune deficiency syndrome'/exp OR 'acquired immune deficiency syndrome' OR 'acquired immunodeficiency syndrome'/exp OR 'acquired immunodeficiency syndrome' OR 'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus') AND ('viral load'/exp OR 'viral load' OR 'viral burden'/exp OR 'viral burden' OR 'viral titer'/exp OR 'viral titer' OR 'virus titer'/exp OR 'virus titer' OR 'cd4 cell count'/exp OR 'cd4 cell count' OR 'cd4 lymphocyte count'/exp OR 'cd4 lymphocyte count' OR 'cd4+ count'/exp OR 'cd4+ count' OR 'cd4 count'/exp OR 'cd4 count' OR 't4 lymphocyte count' OR 'cd4+ cell count'/exp OR 'cd4+ cell count' OR 'cd4 cell counts'/exp OR 'cd4 cell counts' OR 'cd4 lymphocyte counts'/exp OR 'cd4 lymphocyte counts' OR 'cd4+ counts'/exp OR 'cd4+ counts' OR 'cd4 counts'/exp OR 'cd4 counts' OR 't4 lymphocyte counts' OR 'cd4+ cell counts'/exp OR 'cd4+ cell counts') AND (((((('africa south of the sahara'/exp OR 'africa south of the sahara' OR 'botswana' OR 'botswana'/exp OR botswana OR 'burundi' OR 'burundi'/exp OR burundi OR 'ethiopia' OR 'ethiopia'/exp OR ethiopia OR 'zimbabwe' OR 'zimbabwe'/exp OR zimbabwe OR 'mozambique' OR 'mozambique'/exp OR mozambique OR 'malawi' OR 'malawi'/exp OR malawi OR 'zambia'/exp OR 'zambia' OR zambiaor) AND ('tanzania'/exp OR 'tanzania') OR 'tanzania'/exp OR tanzania OR 'kenya' OR 'kenya'/exp OR kenya OR 'uganda' OR 'uganda'/exp OR uganda OR 'rwanda' OR 'rwanda'/exp OR rwanda OR 'senegal' OR 'senegal'/exp OR senegal OR 'gambia' OR 'gambia'/exp OR gambia OR 'guinea' OR 'guinea'/exp OR guinea OR sierra) AND leone OR 'liberia' OR 'liberia'/exp OR liberia OR cote) AND 'd ivoire' OR burkina) AND faso OR 'ghana' OR 'ghana'/exp OR ghana OR 'togo' OR 'togo'/exp OR togo OR 'benin' OR 'benin'/exp OR benin OR 'niger' OR 'niger'/exp OR niger OR 'nigeria' OR 'nigeria'/exp OR nigeria OR 'cameroon' OR 'cameroon'/exp OR cameroon OR 'gabon' OR 'gabon'/exp OR gabon OR 'congo' OR 'congo'/exp OR congo OR 'angola' OR 'angola'/exp OR angola OR 'namibia' OR 'namibia'/exp OR namibia OR 'lesotho' OR 'lesotho'/exp OR lesotho OR 'swaziland' OR 'swaziland'/exp OR swaziland OR 'somalia' OR 'somalia'/exp OR somalia OR 'djibouti' OR 'djibouti'/exp OR djibouti OR 'eritrea' OR 'eritrea'/exp OR eritrea OR 'sudan' OR 'sudan'/exp OR sudan OR 'south* africa' OR 'sub-saharan africa'/exp OR 'sub-saharan africa' OR 'east africa'/exp OR 'east africa' OR 'west africa'/exp OR 'west africa' OR 'central africa'/exp OR 'central africa'))

ADDENDUM 2: EXTENDED METHODOLOGY ON B-COURSE AND DATA SET

B-Course is a web-based data analysis tool for Bayesian Network modelling, in particular dependence and classification modelling. We used both modelling types for our analysis.

Dependency modelling means searching the model of probabilistic dependences of the variables, in which the model searches for a maximal number of correlations with a minimal number of links. Dependencies are represented qualitatively by directed acyclic graphs between variables. Strength of the arcs was scored with a non-parametric bootstrap test. For our data to be of use, we discretized the continuous variables (duration of the study and frequency of home visits) as indicated in our data set. In case of a RCT or comparative cohort study, we also included the comparison arm in the data set. The comparison arm always equalled SOC.

For classification modelling, we had to indicate one classification variable. Since we aimed to investigate which variables contribute to the success of a CHW intervention, we chose 'studies with successful results' as our classification variable. B-course provided us with a list of variables which, according to the data set, were correlated with our classification variable.

Table I Data set used for Bayesian Network modelling

Studies with successful results	Duration of study (short ≤ 6 months = 0; long >6 months = 1)	home visits (0/12m = 0; <12/12m = 1; ≥12/12m = 2)	Adherence support individual	health assessment	HIV education + counselling	adherence support group	ART delivery	social or emotional support	referral to care	HTC	facilitation of clinic visit	adherence assessment	DOT	food provision	transportation stipends for clinic visit	condom distribution
1	0	2	1	1	0	1	0	0	1	0	0	0	0	0	0	0
1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0
1	1	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0
0	1	1	0	0	1	0	0	0	0	1	1	0	0	0	0	0
0	1	1	0	0	1	0	0	0	1	1	0	0	0	0	0	0
0	1		1	1	0	0	0	1	0	0	0	1	0	0	0	0
1	1	2	1	1	1	0	0	0	1	0	0	1	0	0	0	0
0	1	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0
1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0
0	1	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0
1	1	2	1	1	0	0	0	1	0	0	1	0	1	1	1	0
0	1	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0
1	1	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0
1	0		1	0	1	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0

1	1	2	1	1	0	0	1	0	0	0	0	0	0	0	0	0
0	1	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0
0	1	2	1	0	1	0	0	0	0	0	0	0	0	0	0	1
1	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0
0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0
1	1	2	1	1	0	0	0	1	0	0	0	0	1	1	1	0
0	1	2	0	1	0	0	1	0	0	0	0	0	0	0	0	0
0	1	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0
0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0
1	1	2	1	0	1	0	0	0	0	0	0	0	0	0	0	0
1	1	2	1	0	1	0	0	1	0	0	0	0	0	0	0	0

For two studies, we did not find how many home visits were conducted[30,31]. Therefore, we left the number blank.
Abbreviations: ART = antiretroviral therapy; HTC = HIV testing and counselling; DOT = directly observed therapy

ADDENDUM 3: EXCLUDED STUDIES AND ADDITIONAL STUDY

Table II Excluded studies and reason for exclusion

Reference	Purpose	Reason for exclusion
Assefa *et al.* (2012)[32]	To evaluate the effectiveness and acceptability of ART delivery by health officers, nurses and CHWs in Ethiopia, in comparison with ART service in hospitals based on physicians.	Not on task of CHW as per definition of WHO: in the analysis, no distinction has been made between health officers, nurses and CHWs.
Francis *et al.* (2018)[33]	To assess whether community delivery of ART is non-inferior to the standard of care in achieving viral suppression.	Full text not available.
Johnston *et al.* (2012)[34]	To describe second-line ART outcomes in a large workplace- and community-based multi-site programme and to assess whether co-variates available at the time of switch predict early viral suppression on second-line ART.	Not on task of CHW as per definition of WHO: no clear description of community-based program.
Mdege *et al.* (2013)*[35]	To assess the effectiveness of task-shifting and its impact on costs of ART provision.	No consistent reporting of biological HIV outcome.
Nachega *et al.* (2010)[36]	To compare between self-administered ART and treatment-supporter DOT-ART.	Not on task of CHW as per definition of WHO: self-chosen treatment supporters in this study are not CHWs.
Robbins *et al.* (2015)[37]	To examine medication adherence and key psychosocial outcomes among patients who receive either Masivukeni (multimedia technology) or standard of care counselling for ART non-adherence.	No consistent reporting of biological HIV outcome.
Vogt *et al.* (2015)[38]	To assess the effects of community health worker-based defaulter tracing on retention in care and mother-to-child HIV transmission.	No consistent reporting of biological HIV outcome.
Wouters *et al.* (2008)[39]	To assess the impact of baseline health, patient characteristics and community support on ART outcomes	Report on same cohort as other study.

Abbreviations: ART = antiretroviral therapy; DOT = directly observed therapy

*Upon review of the studies referred to in the excluded systematic review of Mdege *et al.*[35], we included one additional study of Chang *et al.*[40]. This study was not found with the original research strategy. The research strategy as described in Addendum 1 did not cover the term 'peer health worker', which is the synonym for community health worker as used in the study of Chang *et al.*

ADDENDUM 4: DETAILS OF INCLUDED STUDIES

Table III Details of included studies

Reference	Setting	Purpose	Study design	Sample	Duration	Tasks of CHWs	Outcomes
Achieng *et al.** (2012)[25]	Kenya	To assess which program components of a program to promote adherence and retention in care during the first 6 months of ART are most effective.	Comparative cohort study: prospective	301 initiating ART	6 months	home visits adherence support individual health assessment adherence support group clinic referral	Time to treatment failure was longer in patients participating in support groups (448 days vs. 337 days, P<0.001), pharmacy counselling (480 days vs. 386 days, P= 0.002), pill counts by physicians (482 days vs. 189 days, P<0.001) and home visits (485 days vs. 426 days, P=0.024).
Bango *et al.** (2016)[21]	South Africa	To assess the effectiveness of lay health worker-led group adherence clubs in comparison with a nurse-driven SOC.	Comparative cohort study: retrospective	6194 stable	12 months	adherence support group ART delivery	Viral suppression in clubs was 99.06% (95% CI 98.82–99.27) for clubs vs. 97.20% (95% CI 96.81–97.56) for SOC.
Barnabas *et al.* (2016)[29]	Uganda & South Africa	To assess whether community-based HIV testing with counsellor support (CHW clinic linkage facilitation or CHW follow-up home visits) and point-of-care CD4 cell count testing would increase uptake of ART in comparison with SOC.	Randomized Controlled Trial	2339	9 months	home visits HIV education HTC facilitation of clinic visits	Roughly a third of the HIV-positive people initiated ART. Overall, 412 of the 483 participants (85%) of them achieved viral suppression by month 9 after enrolment, with no significant differences between interventions and SOC. VL suppression at 9 months was 51% in the group with SOC clinic referral, 52% in the group with CHW clinic facilitation and 47% in the group with CHW follow-up home visits.
Barnabas *et al.* (2014)[41]	Uganda & South Africa	To evaluate initiation of ART and viral suppression after home HTC.	Single arm intervention: implementation study	635	12 months	home visits counselling referral to care HTC	Of 123 ART eligible participants, 94 (76%) initiated ART by 12 months. Of the 77 participants on ART by month 9, 59 (77%) achieved viral suppression by month 12. Among all HIV-positive persons, the proportion with viral suppression (<1,000

							copies/mL) increased from 50% to 65% (P<0.001) at 12 months.
Chang *et al.* (2009)[31]	Uganda	To evaluate the Reach Out program, an alternative AIDS care model led by nurses and peer health workers.	Single arm intervention: retrospective	360	24 months	home visits adherence support individual health assessment social support adherence assessment	Of 360 patients started on treatment, 258 (72%) were active and on therapy approximately 2 years later. Viral load testing demonstrated that 86% of active patients (211/246 tested) had a suppressed VL. The median CD4 increase for active patients was 197 cells per cubic millimetre (interquartile range, 108– 346).
Chang *et al.** (2010)[40]	Uganda	To assess the effect of community-based peer health workers (PHW) on AIDS care	Randomized Controlled Trial	1336 of which 444 (33%) already on ART and 892 (67%) initiating ART	4 years	home visits adherence support individual education + counselling health assessment referral to care adherence assessment	No significant differences were found in cumulative risk of virologic failure (RR 0.81, 95% CI 0.61–1.08) or in shorter-term virologic outcomes (24 weeks virologic failure RR 0.93, 95% CI 0.65–1.32; 48 weeks, RR 0.83, 95% CI 0.47–1.48; 72 weeks, RR 0.81, 95% CI 0.44–1.49). However, virologic failure rates ≥96 weeks into ART were significantly decreased in the intervention arm compared to the control arm (96 week failure RR 0.50, 95% CI 0.31–0.81; 120 week, RR 0.59, 95% CI 0.22–1.60; 144 week, RR 0.39, 95% CI 0.16–0.95; 168 week, RR 0.30, 95% CI 0.097–0.92; 192 week, RR 0.067, 95% CI 0.0065–0.71).
Fatti *et al*.* (2016)[42]	South Africa	To compare clinic-linked community-based adherence support (CBAS) with SOC.	Comparative cohort study: prospective	3861 initiating ART	8 years	home visits adherence support individual referral to care	Amongst patients on ART for 6.5–8 years, proportions not achieving viral suppression were 11.4% and 19.4% in patients with and without clinic-linked community-based adherence support (CBAS), respectively; adjusted risk ratio = 0.47 (95% CI 0.26–0.86; P=0.015). Annual CD4 cell recovery was 15.1 cells/µL/year (95% CI 2.7–27.6) greater in CBAS patients (P=0.017).
Franke *et al*.* (2013)[28]	Rwanda	To examine whether the addition of community-based accompaniment	Comparative cohort study: prospective	610 initiating ART	12 months	home visits adherence support	85% and 79% of participants in the community-based and clinic-based programs, respectively, were retained with

		would improve retention in care, VL suppression, and change in CD4 count, relative to the national model alone.				individual health assessment social support DOT food provision transportation stipends for clinic visits facilitation of clinic visits	viral load suppression at 1 year. Community-based accompaniment was protective against death or loss to follow-up during the first year of ART (hazard ratio, 0.17; 95% CI 0.09–0.35; P<0.0001). Individuals receiving accompaniment were more likely to be retained with a suppressed viral load at 1 year (risk ratio: 1.15; 95% CI 1.03–1.27; P=0.01).
Grimsrud *et al.* (2015)[22]	South Africa	To describe the implementation of CACs at a large, public-sector facility.	Single arm intervention: implementation study	2113 stable	12 months	health assessment adherence support group ART delivery	After 12 months in a CAC, 6% of patients were lost to follow-up and fewer than 2% of patients retained experienced viral rebound.
Igumbor *et al.** (2011)[30]	South Africa	To establish the extent of impact of PA support on patient retention in care, adherence to ART and clinical treatment outcomes.	Comparative cohort study: retrospective	540 initiating ART	6 months	home visits adherence support individual HIV education	The proportion of patients with unsuppressed VLs at 6 months was higher among those without PAs (42%) when compared to the frequency of unsuppressed VLs among patients with PAs (24%; P=0.001). Patients at health facilities with PA services remained in care for longer periods (P=0.001).
Kipp *et al.** (2012)[43]	Uganda	To test the hypothesis that a health-centre community-based ART program can provide a high standard of care and can produce outcomes equivalent to a physician-centred ART model.	Comparative cohort study: prospective	385 initiating ART	24 months	home visits adherence support individual health assessment ART delivery	Successful ART treatment outcomes in the health-centre community-based cohort were equivalent to those in the hospital-based cohort after two years of treatment in on-treatment analysis (VL suppression, 93.0% vs. 87.3%, P=0.12), and in intention-to-treat analysis (VL suppression, 64.9% vs. 62.0%, P=0.560). Patients in the health-centre community-based cohort were more likely to have VL suppression compared to hospital-based patients (adjusted OR= 2.47, 95% CI 1.01–6.04).
Konate *et al.* (2011)[18]	Burkina Faso	To measure treatment outcomes in enhanced program of care.	Single arm intervention:	169 initiating ART	36 months	home visits	47 of 169 HIV-seropositive women initiated ART. 6 months after ART initiation, 79.4% of 34 women had an undetectable plasma VL.

part of population that fulfilled inclusion criteria			implementation study			adherence support individual HIV education condom distribution	This rate was sustained at 18 months (80%, n=30), and 36 months (81.8%, n=22).
Myer *et al.* (2017)[23]	South Africa	To compare effectiveness of CACs with services of primary health clinic on VL, for postpartum women on ART.	Comparative cohort study: prospective, self-chosen (pilot study)	129 post-partum women stable	6 months	health assessment adherence support group ART delivery	There were no differences in VL<1000 copies/mL at 6 months postpartum between women choosing primary health care services (88%) vs. adherence clubs (92%; P=0.483).
Peltzer *et al.* (2012)[26]	South Africa	To assess how a lay health worker led group on ART adherence training might impact on adherence to ART, in comparison with SOC.	Randomized Controlled Trial	152 adherence problems	3 months	adherence support group	Adherence information knowledge increased significantly in the intervention condition in comparison to the SOC, while adherence motivation and skills did not significantly change. There was no significant difference in CD4 cell count, with an increase from 308, ϭ=210 at baseline to 317, ϭ=183 post-intervention in the intervention arm and an increase from 264, ϭ=170 at baseline to 308, ϭ=156 post-intervention in SOC (P=0.412).
Rich *et al.* (2012)[27]	Rwanda	To describe outcomes from a community-based ART program.	Single arm intervention: retrospective medical record review	1041 initiating ART	24 months	home visits adherence support individual health assessment social support DOT food provision transportation stipends for clinic visit	Two years after community-based ART initiation, 961 patients (92.3%) were retained in care, 52 (5%) had died, and 28 (2.7%) were lost to follow-up or had defaulted. Of the 275 with testing at their 2-year anniversary, 232 (84.4%) had <40 copies/ml and 268 (97.5%) had <500 copies/ml.
Selke *et al.* (2010)[24]	Kenya	To assess whether community-based care delivered by people living with HIV/AIDS, aided by an electronic decision support	Randomized Controlled Trial	208 stable	12 months	home visits health assessment ART delivery	After 1 year, there were no significant intervention-control differences with regard to detectable VL (10.5% for the intervention group, 13.5% for the control group, P=0.65), mean CD4 count (404 (265–527) for the

		tool, could replace clinic-based HIV care.				adherence assessment	intervention group, 358 (240–522) for the control group, P=0.50), decline in Karnofsky score, change in ART regimen, new opportunistic infection, or pregnancy rate.
van Rooyen *et al.* (2013)[19] Part of population that fulfilled inclusion criteria	South Africa	To pilot HBCT with point-of-care CD4 count testing and follow-up visits to facilitate linkage of HIV-infected persons to local HIV clinics and uptake of ART.	Single arm intervention: implementation study	137 initiating ART	6 months	home visits HTC	Among the 132 participants not on ART at baseline, 61 were eligible for ART, of whom 36 initiated ART during the study. HIV viral load decreased by 0.49 log10 copies/ml (P=0.009). For the 12 participants eligible for ART (CD4 =<200 cells/mL) at baseline who were not on ART, 11 initiated ART and mean viral load decreased by 3.23 log10 copies/mL (P<0.001).
Weidle *et al.*□ (2006)[44]	Uganda	To assess adherence to antiretroviral therapy in a cohort of HIV-infected people in a home-based AIDS care program.	Single arm intervention: implementation study	987 initiating ART	13-23 months	home visits adherence support individual counselling	Most participants achieved a VL <1000 copies/mL: 894 (98%) of 913 participants in the second quarter and 860 (96%) of 894 in the fourth quarter.
Wouters *et al.** (2009)[12]	South Africa	To investigate how immunological and virologic responses to ART are influenced by patient characteristics, health literacy, baseline CD4 cell count, baseline VL, and three forms of community support (treatment buddy, CHW, support group).	Comparative cohort study: prospective	268	24 months	home visits adherence support individual HIV education emotional support	Baseline health and all three community support initiatives had a positive effect on ART outcomes after 6 months; after 12 and 24 months, community support emerged as the most important predictor of treatment success. There were no significant between-group differences. 76.4% of patients were classified as treatment successes (CD4 cell count =>200 cells/mL and VL <400 copies/mL) after 24 months of ART. At 12 months, all three community support measures were positively associated with the one-year treatment outcome. Patients with a treatment buddy had a greater chance (β= 0.17, P<0.001) of treatment success than patients who lacked such support. The services of a CHW significantly increased a patient's chance of treatment success by 0.16 standard deviations (P<0.01).

	Participating in a support group also had a positive effect on the treatment outcome, because these patients were significantly more likely (β=0.12, P<0.001) to have an undetectable viral load and a CD4 cell count above 200 cells/mL

**Statistically significant effect of CHW intervention on biological HIV outcomes in comparison with SOC.*

Viral load suppression in at least 90 percent of patients

Abbreviations: ART = antiretroviral therapy; SOC = Standard of Care; HTC = HIV testing and counselling; VL = viral load; CACs = community-based adherence clubs; PA = patient advocate

ADDENDUM 5: ORIGINAL EXPLORATIVE DEPENDENCY MODEL AS CREATED BY B-COURSE

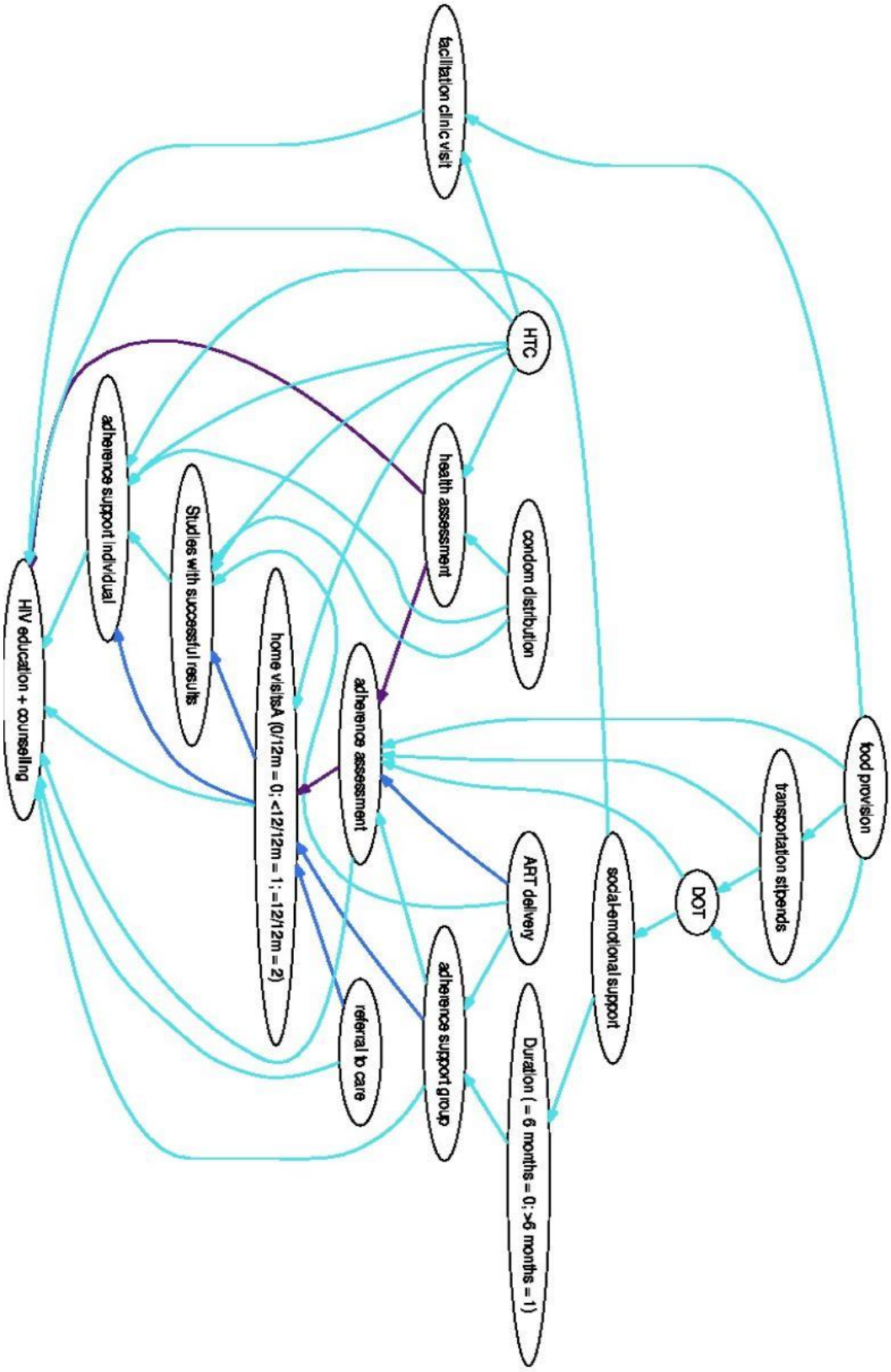

Figure I Original explorative dependency model as created by B-course
The darker the arks, the stronger the connection between the variables. The direction of the arrows is meaningless.