WHO/HIV/2013.129

ANNEX 4: Systematic review – ALHIV: Disclosure, adherence and retention in care

Disclosure

Adolescent disclosure of HIV status

Narrative of results and findings, with evidence quality

PICO 3a. Should adolescents with HIV infection disclose their HIV status to parents, family members, sexual partners, others?

3a. Results, Quality of the evidence, Findings

Inclusion criteria included controlled trials (randomized or not), pre-post-intervention evaluations and observational (retrospective or prospective) studies in which there is a comparator. No controlled trials were identified to address PICO 3a. Because of the expected paucity of adolescent studies, study design criteria were broadened to include adult studies. Of the 29 publications (27 distinct studies) included after removal of studies not eligible for inclusion and duplicates, nine were from high-income countries and 18 from low or middle-income countries. Adolescents were defined as ten through 19 years of age. Only three studies were of adolescents (Dempsey 2012, Lam 2007, Sherman 2000). The remaining studies described adults.

None of the evidence for PICO 3a could be subjected to GRADE analysis, for the following reasons. Two of the three adolescent studies were cross-sectional (Dempsey 2012, Lam 2007). The third was a prospective observational study that compared the difference in mean immunologic and behavioural test results between children (age 8 to 18 years old) who had and had not disclosed their HIV status (Sherman 2000). All but three adult studies used a cross-sectional, descriptive, or case control design, and thus were not amenable to GRADE analysis. The remaining three were cohort studies but presented insufficient information needed for GRADE analysis because they reported only hazard ratios (Chepkurui 2012), regression parameters (Strachan 2007), or outcomes (prevention of maternal-to-child transmission [PMTCT] outcomes) not pre-specified for this PICO question (Jasserson 2011). Therefore, associations are described below, without measures of effect or confidence intervals.

Overall, the adolescent studies showed that disclosure was associated with increased percent of CD4 cells (Sherman 2000), decreased number of partners (but not with decreases in unprotected sex) (Dempsey 2012), and increased distress when disclosure was to acquaintances, but no statistically significant association with mental health symptoms with disclosure to family or close friends (Lam 2007).

Seven studies of adults showed disclosure was associated with linkage to care and ART adherence (Sayles 2006, Beyene 2009, Ochieng-Ooko 2010, Rotheram-Borus 2010, Abaynew 2011, Ding 2011, Hatcher 2012), but one showed no association (Skogar 2006). Other studies showed disclosure was

associated with higher CD4 counts (Strachan 2007), and nondisclosure was associated with virologic failure at 48 weeks (Chepkurui 2012). Disclosure was associated with better HIV testing and nevirapine adherence in infants (Peltzer 2010, Peltzer 2011), and nondisclosure was associated with suboptimal PMTCT outcomes (Jasserson 2011).

Other studies of adults reported on the following additional outcomes. Disclosure to sexual partners was associated with increased frequency of condom use and reduced number of sexual partners; those who disclosed to HIV-negative partners were significantly less likely to engage in unprotected anal sex compared to those who did not disclose their HIV status (Sixgashe 2001, Crepaz 2003, Kebede 2005, Parsons 2005, Wong 2009, Bird 2011, Seid 2012). One study of adult women of three ethnic groups in the US found no association between disclosure and depressed mood or health-related psychological distress, except among Latinas in whom a modest association was found (Comer 2000). In four studies of adults, disclosure was associated with higher levels of HIV stigma; women who disclosed to sexual partners reported negative experiences such as anger and blame, including one study where women reported that partners reacted with violence and ending the relationship (Kilewo 2001, Kebede 2005, Gari 2010, Holzemer 2012).

PICO 3b: What is the best way to support adolescents to disclose their HIV status safely and effectively?

3b.1 Results of seven studies amenable to GRADE analysis

Seven studies were amenable to GRADE analysis, of which five of which were controlled trials (Rotheram-Borus 2001a, Rotheram-Borus 2001b, Wolitski 2005, Murphy 2011, Serovich 2011) and two were cohort studies (Mundell 2011, Otis 2012). Only one was conducted of HIV-infected adolescents.(Rotheram-Borus 2001a) These seven studies are described below, based on type of intervention utilized to support disclosure of positive HIV status.

Small group discussions or group counselling (USA). A randomized controlled trial including HIV-infected adolescents was conducted in a high-income country (USA) in the pre-antiretroviral therapy era, and utilized small group discussions to support disclosure (Rotheram-Borus 2001a). In comparing adolescents exposed to the intervention and those in standard care, no statistically significant differences were observed in disclosure to sex partners at 15 months (RR 1.2, 95% CI 0.79 to 1.6), mean T-cell count (MD 8.4 higher, 95% CI 12.58 lower to 29.38 higher), emotional distress scores at 9 or 15 months (MD 0 higher 95% CI 0.42 lower to 0.42 higher; the same at each interval), or mean physical disease score at 15 months (MD 0.1 lower, 95% CI 0.52 lower to 0.32 higher). Participating adolescents had significantly more missed appointments at 9 months, compared to those receiving standard care (MD 0.6 higher, 95% CI 0.18 to 1.02 higher). However, adolescents participating in small group discussions were less likely to report unprotected sex compared to those receiving standard care (RR 0.15, 95% CI 0.03 to 0.73).

In an RCT conducted in the USA in the pre-antiretroviral therapy era (Rotheram-Borus 2001b), HIV-infected parents participating in small group discussions with their adolescent children had higher mean depression scores at 3 months (MD 0.28 higher, 95% CI 0.06 to 0.5 higher), but lower mean depression scores at 15 months (MD 0.22 lower, 95% CI 0.44 lower to 0 higher) and 24 months (statistically non-significant) (MD 0.12 lower, 95% CI 0.34 lower to 0.1 higher) (Rotheram-Borus 2001b). No statistically significant differences were observed when comparing intervention to control groups with respect to

disclosure of HIV status to at least one adolescent at 24 months (RR 1.04, 95% CI 0.96 to 1.14) or to disclosure of HIV status to all children at 24 months (RR 1, 95% CI 0.91 to 1.1). Note: Lower scores indicate less depression.

In an RCT of group counselling by trained facilitators in the USA (Serovich 2011), HIV-infected adult men who have sex with men (MSM) were not significantly more likely to disclose to a higher number of family members than were the wait-list controls (RR 1.1, 95% CI 0.91 to 1.34).

Structured support groups or workshops (Africa). Two observational studies evaluated structured groups or workshops to support disclosure by adult HIV-infected women. In a South Africa study (Mundell 2011), more HIV-infected pregnant women who participated in structured support groups had disclosed their HIV status at two months of follow up (RR 1.2, 95% CI 1.09 to 1.32) and at eight months of follow up (RR 1.18, 95% CI 1.09 to 1.28) compared to before attending the support groups. However, there was no difference in participants' report of feelings of depression at eight months compared to reports obtained before attending the support groups (RR 1, 95% CI 0.92 to 1.08). In an observational study evaluating the effect of empowerment workshops for HIV-infected women in Mali (Otis 2012), no difference was observed between pre- and post-intervention mean scores for the weight of keeping their HIV status a secret (MD -1.07 lower, 95% CI -1.3 lower to 0.81 higher).

One-on-one counselling. In an RCT conducted in the USA (Murphy 2011), adult HIV-infected mothers participating in four-session, one-on-one counselling were more likely to disclose their HIV status to their children (ages 6 to 12 years old), compared to those receiving standard care (RR 4.56, 95% CI 1.4 to 14.77).

Peer-led behavioural interventions. An RCT to evaluate the effectiveness of peer-led behavioural sessions on disclosure and related behavioural outcomes was conducted in the USA (Wolitski 2005) with HIV-infected adult MSM. No statistically significant difference was observed between intervention and control groups with regard to disclosure – neither to some sex partners (RR 1.06, 95% CI 0.85 to 1.32) or to all sex partners (RR 1.04, 95% CI 0.87 to 1.25). No statistically significant difference was observed between groups in sexual behaviour, including unprotected anal intercourse (RR 0.87, 95% CI 0.69 to 1.1), or consistent condom use during insertive anal intercourse (RR 1.03, 95% CI 0.8 to 1.34). MSM participating in peer-led behavioural sessions had a higher mean score in reporting that the intervention had motivated them to inform their sex partners of HIV status, compared to participants receiving standard care (MD 0.57 higher, 95% CI 0.41 to 0.73 higher).

3b.2. Findings of the seven studies amenable to GRADE analysis

Small group discussions or group counselling (USA) for supporting disclosure was shown in a trial of HIV-infected adolescents to significantly decrease the adolescents' report of unprotected sex, but there was no statistically significant difference in disclosure of HIV status to sexual partners (Rotheram-Borus 2001a). When small group discussions were used to support disclosure by HIV-infected parents (Rotheram-Borus 2001b), there was no significant increase in disclosure to their adolescent children, and the parents had significantly higher mean depression scores at 3 months (but no significant difference at 15 or 24 months). HIV-infected adult MSM were no more likely to disclose to a higher number of family members (statistically non-significant) than was the wait-list control group (Serovich 2011).

Structured support groups or workshops (Africa) were shown to significantly increase disclosure by HIV-infected pregnant women at two and eight months of follow up, but there was no statistically significant difference in reported depression (Mundell 2011). Another study (Otis 2012) found no significant difference one week after HIV-infected women participated in empowerment workshops for the weight of keeping their HIV status a secret.

One-on-one counselling was shown to significantly increase disclosure by HIV-infected mothers to their young children (Murphy 2011).

Peer-led behavioural interventions were shown to significantly increase adult MSM's self-reported motivation to inform sexual partners (Wolitski 2005).

3b.3. Quality of the evidence for the seven studies amenable to GRADE analysis

In the GRADE system, well-conducted RCTs (without additional limitations) provide high quality evidence, and observational studies without any special strength (and without additional limitations) provide low-quality evidence. In this analysis, we found five controlled trials and two cohort studies which provided very low quality evidence for the benefits of several methods for supporting disclosure of HIV status. The evidence for all outcomes was very low quality evidence due to serious indirectness (studies conducted in adults, and/or in the USA), and serious or very serious imprecision (small number of events reported).

Small group discussions or group counselling sessions were found to significantly reduce unprotected sex in adolescents with HIV (Rotheram-Borus 2001a), and to significantly decrease depression in the short term in HIV-infected parents (Rotheram-Borus 2001b). However, these interventions resulted in no statistically significant increase in disclosure by HIV-infected adolescents to their sexual partners, HIV-infected parents to their children, or HIV-infected MSM to family members. The estimates of effect are very uncertain from these controlled trials. The quality of evidence is very low due to serious or very serious imprecision (few or very few events) and serious indirectness (studies were conducted in a high-income country, and two were conducted in HIV-infected adults rather than adolescents).

Structured support groups or workshops in Africa significantly increased disclosure by HIV-infected pregnant women (Mundell 2011), but there was no statistically significant difference in reported depression (Mundell 2011) or perceived weight of keeping their HIV status a secret (Otis 2012). The quality of evidence is very low from these two observational studies. Evidence quality was graded down for indirectness (adult population), and serious imprecision (few events).

One-on-one counselling was found to significantly increase disclosure by HIV-infected mothers to their young children (Murphy 2011), but this is very low quality evidence. This randomized controlled trial provides a very uncertain estimate of effect because of very serious imprecision (very few events) and serious indirectness (study conducted in a high-income country, and in HIV-infected adults rather than adolescents).

A peer-led behavioural intervention was shown to significantly increase adult MSM's self-reported motivation to inform sexual partners (Wolitski 2005). The quality of evidence is very low, so this measure of effect is very uncertain. Evidence quality from this randomized controlled trial was graded down for very serious indirectness (adult population, study was conducted in the United States, and self-reported data), and serious imprecision (few events).

3b.4. Summary of nine studies not amenable to GRADE analysis

Nine additional studies were included but were not amenable to GRADE analysis because of inadequate data. Four were conducted in the USA, one in Ethiopia, one in Haiti, one in Nigeria, and two in South Africa. Only one addressed HIV-infected adolescents; the remaining studies were of HIV-infected women or MSM. One study was a disclosure-only intervention (Serovich 2009); the remaining were more comprehensive interventions designed to address multiple issues relating to HIV infection.

Studies in adolescents

Small group discussions. There was limited evidence from the one adolescent study (Smith Fawzi 2012) that professional-led small group sessions had a positive effect on the adolescents' mental health.

Studies in adults

Small group discussions. A cluster randomized controlled trial of HIV-infected pregnant women found small group teaching by peer mentors resulted in increased preventive behaviours, decreased maternal depression, and better infant outcomes (Rotheram-Borus 2012). A randomized controlled trial found professional and peer-led support groups increased condom use in low-income HIV-infected women (Teti 2010).

Community-based interventions with disclosure component. Dewo (2012) found that HIV-infected adults had reduced loss to follow up and improved retention after receiving support from case managers, adherence counsellors, and community volunteers. Wouters (2009) found that HIV-infected adults with community health worker support were significantly more likely to disclose their serostatus to family members.

Individual counselling-based interventions. Olley (2006) found that adults with new HIV infection had a significant decrease in depression scores four weeks after assessment, and a significant increase in their intention to disclose their status. Patterson (2003) found that HIV-infected adults who reported unprotected sex with an unknown partner all showed a reduction in unprotected sex, regardless of their randomized assignment to intervention or control groups.

Online, computer-based interventions. Chiasson (2009) found that HIV-infected and uninfected MSM had no difference in HIV disclosure but were less likely to report a new or casual sexual partner or unprotected anal intercourse compared to before the intervention. Serovich (2009) found that HIV-infected MSM had improved disclosure behaviours after facilitated administration of an intervention tailored for disclosure to casual sexual partners.

Training for health workers

Can training of health care providers in adolescent health improve retention and adherence among adolescents living with HIV?

Training of health care providers in adolescent health for improving retention and adherence among adolescents living with HIV infection

1.1 Results

No studies were found evaluating the training of health workers who provide care and treatment to adolescents living with HIV, and the effect of this training on pre-specified adolescent health outcomes and quality of care outcomes for adolescents living with HIV infection.

However we did identify three studies that did not meet inclusion criteria but which inform this research question. Two randomized control trials (RCT) and one serial cross-sectional study were identified that evaluated the training of health workers providing care to adolescents with other chronic care needs (asthma, diabetes, and reproductive health services, respectively), and report the effect of this training on adolescent health outcomes and quality of care outcomes.

Asthma. The first intervention was published in one manuscript (Lozano 2004). The peer leader RCT intervention consisted of training one physician per practice in asthma guidelines and peer teaching methods. The planned care arm combined the peer leader intervention with nurse-mediated organizational change through planned visits with assessments, care planning and self-management support in collaboration with physicians. The trial randomized children ages 3-17 years of age living with asthma in the United States to a planned care intervention arm (n=213), a peer leader intervention arm (n=226) or a control arm of standard care (n=199).

Diabetes. The second intervention, "Talking Diabetes," was published in two manuscripts (Robling 2012; Gregory 2011). The RCT involved training providers in agenda-setting, guiding communication style and a flexible menu of consultation strategies to support patient-lead behavior change. The trial randomized youth ages 4-15 living with diabetes in the United Kingdom to the intervention arm (n=399) or to a standard care control arm (n=334).

Reproductive health services. The third intervention was published in a grey literature report (ICRW 2012). This study looked at the effect of using the World Health Organization (WHO) Orientation Programme on Adolescent Health for Health Care Providers (OP) and the Adolescent Job Aid (AJA) program to build the capacity of health workers globally to respond to adolescent and young clients effectively. To evaluate the use of these tools, an intervention was conducted in early 2009 in two districts in the state of Gujarat, India among young women aged 15-25 years receiving reproductive health services at primary healthcare centers. Medical officers (MO) received a five-day training on the use of the OP and the AJA and an evaluation was then conducted to assess the effectiveness of this training. One district served as the control district and the other as the intervention district. A total of 40 MO were trained in the intervention district with 28 participating in the follow-up measure. Client exit interviews were conducted in the intervention arm (n=230 at baseline, n=140 at follow-up) and the control arm (n=155 at baseline, n=195 at follow-up). Observations of MO practices were conducted in the intervention arm (n=123 at baseline, n=85 at follow-up) and the control arm (n=108 at baseline and n=119 at follow-up). Follow-up was conducted at 4-5 months.

1.2 Findings

Asthma. The intervention training health workers in asthma care for youth found that the planned care intervention did have a significant effect on asthma symptom days compared to the control arm and a

trend favoring the peer leader intervention compared to the control arm. Both intervention arms had lower oral steroid burst rates compared to the control arm. The authors concluded that planned care is an effective model for improving asthma care in the primary care setting, and while peer leader education on its own may also work it is much less comprehensive than planned care.

Diabetes. The intervention training health workers in diabetes care for youth found that training diabetes care teams had no effect on HbA1c levels (a marker for diabetes control) or on self-reported adherence to diabetic medications. The authors reported that improving glycemic control in children attending specialist diabetes clinics might not be possible through brief, team-wide training in consultation skills.

Reproductive health services. The reproductive health services intervention found that MOs in the intervention district increased in their belief that health problems of young female clients not only stemmed from their sexual activity, but were also due to their lack of awareness about their sexual health (21 MOs at baseline versus 27 MOs at follow-up) ($p<0.05$). Some of this knowledge increase was also seen in the control district. They also found that compared to the control district, MOs in the intervention had a better understanding of the need to ensure client privacy. MOs in the intervention condition showed improvement in all areas recommended for care of young female clients, including improvements in pre-examination explanations, physical examinations, complaint assessment and case management. More MOs in the intervention arm were found to be sensitive to the need to spend time building rapport with their clients and gaining their confidence. However, no difference was found between baseline and follow-up for trained MOs in regards to their case management practices. Significantly, more clients showed confidence in their provider at follow-up and reported having greater privacy during the interactions, including an examination in a separate room. Clients from the intervention arm were more likely to report that they understood information given to them by the MO and fewer clients reported this in the control arm (81% in the intervention arm vs. 69% in the control arm at follow-up). Overall, client satisfaction with the services and information received and ease of following advice increased from 62% at baseline to 81% at follow-up ($z=3.69$, $p<0.05$).

1.3 Quality of the evidence

The overall quality of this evidence is very low due to the very serious indirectness of the populations studied to the present review question, the heterogeneity of the outcomes reported, and the relatively small sample sizes. GRADE evidence profiles were not created for this review.

Community-based approaches

Can community-based approaches improve adherence to treatment and retention to care among adolescents?

Community-based approaches to improve adherence amongst adolescents
Narrative of results and findings with evidence quality

Our search yielded a total of 656 records. After removing 116 duplicates, we screened 540 records, and reviewed 79 full-text articles. Twenty-seven were determined to be eligible for inclusion in this review. Of the 27 publications included, 17 were amenable to inclusion in GRADE analysis. The remaining 10 could not be analyzed with GRADE because they presented insufficient information needed for GRADE analysis (Igumbor 2011; Stubbs 2009), had no comparator or because the comparator was not the comparator of interest (Achieng 2012; Bekker 2006; Chang 2009; Kipp 2010; Kipp 2011; Nglazi 2011; Nglazi 2012; Rich 2012).

Interventions described included: home visits by community/lay health workers who conducted health assessments, provided education and/or support, and made referrals (Fatti 2012; Grimwood 2012; Kabore 2010; Kipp 2012; Munoz 2011; Williams 2006); use of mobile health (mHealth) technologies (e.g., cellular phones, pagers) for home visitors to communicate about the index patients' health and adherence to a centralized database, or for peers to communicate with each other (Chang 2010; Chang 2011; Selke 2010; Simoni 2009) ; socioeconomic support (Talisuna-Alamo 2012) ; peer support (e.g., "mentor mothers", treatment partners) (Futterman 2010; Simoni 2007; Simoni 2009; Taiwo 2010) ; and community-based, directly administered antiretroviral therapy (DAART) (e.g., directly observed therapy via mobile outreach units, home-based directly observed therapy by lay health worker) (Altice 2007; Macalino 2007; Pearson 2007). Reported effects of these interventions are described by outcome below.

Results of 17 studies included in GRADE analysis

Of the 17 records eligible for inclusion n GRADE analysis, five reported on studies conducted in the USA (Altice 2007; Macalino 2007; Simoni 2009; Simoni 2007; Williams 2006), and 12 reported on studies conducted in low- and middle-income countries including Botswana, Lesotho, Kenya, Mozambique, Namibia, Nigeria, Peru, South Africa and Uganda. None of the studies focused on adolescent populations. One of the studies was focused on children under age 16 years (Grimwood 2012). The remainder included adult populations only, including general adult populations on ART (Chang 2010; Chang 2011; Fatti 2012; Kabore 2010; Kipp 2012; Munoz 2011; Pearson 2007; Selke 2010; Taiwo 2010; Talisuna-Alamo 2012; Simoni 2007; Simoni 2009; Williams 2006); pregnant women (Futterman 2010), and injection drug users (Altice 2007; Macalino 2007). Ten of the studies were randomized controlled trials (Altice 2007; Chang 2010; Chang 2011; Macalino 2007; Pearson 2007; Selke 2010; Simoni 2007; Simoni 2009; Taiwo 2010; Williams 2006). The remaining seven were observational studies (Futterman 2010; Fatti 2012; Grimwood 2012; Kabore 2010; Kipp 2012; Munoz 2011; Talisuna-Alamo 2012). The results are described below by outcome and intervention type.

1. Adherence

Eleven of the 17 studies (nine RCTs, two observational) provided data regarding the efficacy or effectiveness of a community-based intervention on antiretroviral therapy (ART) adherence.

I. Home-based health assessment, education and support by community health workers

One RCT conducted in the USA (Williams 2006); and two prospective cohort studies – one conducted in Peru (Munoz 2011) and one multi-site study including participants in Botswana, Lesotho, Namibia, and South Africa (Kabore 2010) – provided data examining the effectiveness of interventions in which lay,

paraprofessional and/or professional health workers provided home-based health assessments, education, and/or support to HIV-infected individuals on improving ART adherence. All of the studies included adult populations only. Adherence level was associated with exposure to home-based support services in one study (Kabore 2010), but not in the others (Munoz 2011; Williams 2006).

In Kabore 2010, a greater proportion of participants who received home-based care and food support demonstrated better ART adherence, compared to participants who received no community services (RR 1.15, 95% CI 1.03 - 1.27). However, Williams (2006) did not show a statistically significant intervention effect on ≥90% adherence (RR 1.53, 95% CI 0.79 - 2.95). Similarly, one prospective cohort study evaluating the efficacy of tailored home-based ART support, microfinance and/or psychosocial support (Munoz 2011) found no statistically significant difference in adherence between participants exposed to the intervention and their matched controls at 2 years of follow-up (RR 1.05, 95% CI 0.88 to 1.27).

II. mHealth support intervention used by peers or community health workers at home visits

One RCT conducted in the USA (Simoni 2009), two cluster-RCTs conducted in Uganda (Chang 2010; Chang 2011), and one cluster-RCT conducted in Kenya (Selke 2010) provided data examining the effectiveness of community-based interventions in which mobile health (mHealth) technology was used on improving ART drug adherence. None showed significant differences in adherence between intervention and control groups, regardless of the percentage used for measure optimal adherence.

Simoni 2009 compared participants assigned to one of four study arms: group 1: peer support involving 6 twice monthly 1-hour peer meetings and weekly phone calls from peers to participants; group 2- pager messaging including customized messages to remind the participant to take their medication, provide educational information about medications, and assess adherence; group 3- both strategies; or group 4- usual care (control group). There was no statistically significant difference in mean 1-week adherence at 6 months (MD 5.6% lower [21.39% lower to 10.19% higher]) or at 9 months (MD 3% higher [11.83% lower to 17.83% higher]) in the peer+pager group compared to the control group.

Selke 2010 examined the effectiveness of home visits in which peer health workers ("Community Care Coordinators " [CCC]) used a Personal Digital Assistant (PDA) which provided prompted guidance to the CCC concerning patient symptoms and adherence assessment and delivered alerts as indicated by the entries made. There was no statistically significant difference in adherence level at 12 months follow-up between participants in the intervention compared to the control group (RR 0.93, 95% CI 0.82 to 1.06).

Chang 2010 and Chang 2011 examined the effectiveness of home visits in which peer health workers used a mobile phone and tasked to use text messaging or send home visit data back to a central clinic. Using "less than 95% adherence" (<95%) as the measure, no significant difference in adherence was observed at 26 months (RR 0.57, 95% CI 0.23 to 1.37, Chang 2010; RR 0.24, 95% CI 0.05 to 1.07, Chang 2011). Using 100% adherence as the cut-off for optimal adherence, no significant difference in adherence was observed at 26 months (RR 1.09, 95% CI 0.87 to 1.37, Chang 2010; RR 0.98, 95% CI 0.78 to 1.23, Chang 2011).

III. Socioeconomic support

Not assessed.

IV. Peer support

Two RCTs conducted in the USA (Simoni 2007; Simoni 2009) and one RCT from Nigeria (Taiwo 2010) provided data on the efficacy of peer support interventions on improving ART drug adherence. Taiwo 2010 showed that HIV-infected adults randomized to receive support from a patient-selected treatment partner had significantly higher rates of adherence at 48 weeks follow up compared to patients randomized to standard care (RR 1.19, 95% CI 1.07 to 1.33). Simoni 2007 and Simoni 2009 compared ART adherence between HIV-infected adults randomized to participate in six twice-monthly one-hour group meetings at the clinic with peers and other study participants as well as weekly phone calls from peers to participants to HIV-infected adults who received standard care. No statistically significant difference in mean 3-day adherence level was observed at three months (MD 0 higher [13.49 lower to 13.49 higher) or six months (MD 8.1 lower [23.2 lower to 7 higher]). No significant difference in mean 1-week adherence was observed at three months (MD 8.3 higher [7.78 lower to 24.38 higher]) (Simoni 2007), or six months (MD 3.8 lower [20.05 lower to 12.45 higher]) (Simoni 2009). No significant difference in mean 4-week adherence was observed at three months (MD 2.9 lower [18.47 lower to 12.67 higher]), or 6 months (MD 3.3 lower [18.96 lower to 12.36 higher]) (Simoni 2007).

V. Community-based DAART

One RCT conducted in Mozambique (Pearson 2007) and one RCT conducted in the US (Altice 2007) provided data examining the effectiveness of community based DAART on improving ART adherence. Neither showed significant differences in adherence between intervention and control groups, regardless of the cut-off used for determining optimal adherence or length of follow up. Pearson 2007 compared HIV-infected adults randomized to receive six weeks of daily peer-delivered, modified directly observed therapy to those who received standard care showed no statistically significant difference in >90% adherence level at the 12- month follow up between intervention and control groups (RR 1.09, 95% CI 0.99-1.18). Altice 2007 compared HIV-infected drug users randomized to receive directly administered ART (DAART) to those who received standard care showed no statistically significant difference in $\geq$80% adherence level at 6-month follow up between intervention and control groups (RR 1.18, 95% CI 0.9 to 1.56).

2. Mortality

Ten of the 17 studies (five RCTs, five observational) provided data regarding the efficacy or effectiveness of a community-based intervention on mortality.

I. Home-based health assessment, education and support by community health workers

Four observational studies examined the effectiveness of home-based health assessment, education and support provided by community health workers on mortality (Fatti 2012; Grimwood 2010; Munoz 2011; Kipp 2012).

Two studies conducted in South Africa showed significant reductions in mortality amongst participants who received home-based health assessment, education, and support by community health workers (Fatti 2012; Grimwood 2010). Grimwood 2010 evaluated a home-based CHW adherence and psychosocial support for caregivers of HIV-infected children under 16 years of age who initiated ART. In

this study, there was a statistically significant reduction in mortality at 3 years of follow up amongst children in CHW-supported households compared to children residing in households that did not receive home-based support (RR 0.46, 95% CI 0.26 to 0.82). Fatti 2012 evaluated CHW-provided home-based adherence and psychosocial support for HIV-infected adults on ART. There was a significant reduction in mortality at 5 years of follow up amongst participants in the intervention group compared to those in the control group (RR 0.85, 95% CI 0.81 to 0.89).

Two studies showed no intervention effect on mortality (Kipp 2012; Munoz 2011). Munoz 2011, conducted in Peru, evaluated the effectiveness of tailored home-based support including DOT-HAART, microfinance and/or psychosocial support. Crude mortality was higher amongst participants exposed to the intervention compared to their matched controls at 2 years follow-up, but the difference was not statistically significant (RR 1.18, 95% CI 0.49 to 2.85). Kipp 2012, conducted in Uganda, evaluated outcomes of patients enrolled to care in a community-based ART program compared to patients enrolled to care at a well-established hospital-based ART program. Crude mortality was higher in the community-based cohort compared to the hospital-based cohort, but the difference was not statistically significant (RR 1.5, 95% CI 0.91 to 2.47).

II. mHealth support intervention used by peer health workers at home visits

Two cluster-RCTs conducted in Uganda (Chang 2010; Chang 2011) and one cluster-RCT conducted in Kenya (Selke 2010) examined the efficacy of mHealth-supported home visits on mortality. No significant difference in mortality at 26 months was observed between HIV-infected adults who received home visits by peer health workers using a mobile phone for text messaging or to send home visit data back to a central clinic, compared to HIV-infected adults who received home-based support by a peer health worker not using mHealth support (RR 1.1, 95% CI 0.74 to 1.62, Chang 2010; RR 0.82, 95% CI 0.55 to 1.22, Chang 2011). In Selke 2010, there were no deaths in the intervention or control arms.

III. Socioeconomic support

One observational retrospective cohort study assessed the effectiveness of providing one or more types of socioeconomic support on mortality (Talisuna-Alamo 2012). This study found a significantly decreased risk of mortality follow up at 10 years amongst adults who received two or more types of socioeconomic support compared to adults who received no support (RR 0.49, 95% CI 0.38 to 0.64). However, there was not a statistically significant difference in mortality rates between patients who received one type of socioeconomic support compared to those who received no support (RR 0.96, 95% CI 0.85 to 1.09).

IV. Peer support

One RCT conducted in Nigeria found higher crude mortality amongst HIV-infected adults who received support from a patient-selected treatment partner to participants randomized to standard of care, but the difference was not statistically significant (10.6% vs 6.1%, RR1.74, 95% CI 0.95-3.2) (Taiwo 2010).

V. Directly observed ART (DAART)

One RCT from Mozambique (Pearson 2007) found there to be no difference in mortality amongst HIV-infected adults randomized to receive six weeks of daily peer-delivered, modified directly observed therapy compared to HIV-infected adults who received standard care (RR0.72, 95% CI 0.44-1.18).

3. Viral Failure /Viral suppression

Eleven of the 17 studies (eight RCTs, three observational) provided data regarding the efficacy or effectiveness of a community-based intervention on viral suppression or viral failure.

I. Home-based health assessment, education and support by community health workers

Three studies examined the effectiveness of home-based adherence and health promotion support by community health workers on virologic suppression (Fatti 2012; Kipp 2012; Munoz 2011). One of the three studies showed significant improvements in virologic suppression amongst intervention participants. Fatti 2012 examined the effectiveness of CHW-provided home-based adherence and psychosocial support for HIV-infected adults on ART on viral suppression at 6- and 24- months. There was a significant improvement in viral suppression in the intervention group compared to the control group at 6 months (RR 1.06, 95% CI 1.05 to 1.08), 12 months (RR 1.18, 95% CI 1.15 to 1.21), and 24 months (RR 1.26, 95% CI 1.21 to 1.31). Kipp 2012 found there to be no statistically significant difference in viral suppression between patients enrolled to care in a community-based ART program compared to patients enrolled to care at a well-established hospital-based ART program (RR 1.07, 95% 0.98 to 1.15). Munoz 2011 found there to be no statistically significant difference in viral suppression between participants who received home-based support including DOT-ART, microfinance and/or psychosocial support (RR 1.49, 95% CI 0.97 to 2.29).

II. mHealth support intervention used by peer health workers at home visits

One cluster-RCT conducted in Kenya (Selke 2010) , two cluster-RCTS conducted in Uganda (Chang 2010; Chang2011) and one RCT conducted in the USA (Simoni 2009) examined the impact of mHealth-supported home visits on viral failure or suppression. None showed a significant improvement in virologic suppression or reduction in virologic failure. Chang 2010 showed there to be no effect of the intervention on viral failure when measured at 24 weeks (RR 0.94, 95% CI 0.56 to 1.57) or 48 weeks (RR 0.84, 95% CI 0.5 to 1.42), but did show a significant reduction in viral failure at 96 weeks amongst participants in the intervention arm compared to those in the control arm (RR 0.51, 95% CI 0.29 to 0.92). Chang 2011 also showed there to be no effect of the intervention on viral failure when measured at 24 weeks (RR 1.59, 95% CI 0.91 to 2.79) or 48 weeks (RR 0.95, 95% CI 0.53 to 1.17). Selke 2010 showed there to be no difference in the proportion of patients with viral failure in the intervention compared to those in the control arm (RR 0.81, 95% CI 0.36 to 1.81). 2009 found no statistically significant difference in mean viral load level at 3 months (MD 0.4 lower [1.01% lower to 0.21 higher]) or at 6 months (MD 0 higher [0.62 lower to 0.62 higher]) in the peer+pager group compared to the control group.

III. Socioeconomic support

Not assessed.

IV. Peer support

One RCT conducted in Nigeria (Taiwo 2010) and two RCTs conducted in the USA (Simoni 2007; Simoni 2009) assessed the efficacy of peer-support interventions on mean viral load or viral suppression. None showed an intervention effect on viral load/viral suppression. Taiwo 2010 found there to be no difference in viral suppression amongst HIV-infected adults randomized to receive support from a patient-selected treatment partner compared to participants randomized to standard of care at 24 weeks (RR 1.16, 95% CI 1 to 1.35) or 48 weeks follow up (RR 1.01, 95% CI 0.89 to 1.14). Simoni 2007and

Simoni 2009 showed no statistically significant difference in mean viral load level at three months (MD 0.28 higher [0.27 lower to 0.84 higher]), six months (MD 0.72 higher [0.14 lower to 1.29 higher]), or at nine months (MD 0 higher [0.72 lower to 0.72 higher]).

V. Community-based DAART

Two RCTs conducted in the USA with HIV-infected adult substance users examined the efficacy of community-based DAART on viral suppression (Altice 2007; Macalino 2007). Macalino 2007 showed community based DAART to be associated with reduced viral load at 3 months follow up in the intervention group compared to the control group (RR 1.71, 95% CI 1.05 to 2.76). A second study (Altice 2007) showed there to be no difference in viral suppression at 6 months follow up (RR 1.24, 95% CI 0.95-1.63).

5. Retention on 1st line regimen

One of the 17 studies (an RCT) provided data regarding the efficacy of a community-based intervention on retention of the 1st line ART regimen. This RCT, conducted in the US, showed there to be no statistically significant difference in retention on first-line regimen at six months amongst HIV-infected injection drug users who received directly observed ART compared to injection drug users who received standard care (RR 1, 95% CI 0.69-1.46) (Altice 2007).

6. Follow-up visits

One of the 17 studies (an observational study) provided data regarding the effectiveness of a community-based intervention on attendance at follow-up medical visits. This non-randomized comparative prospective cohort study conducted in South Africa found no difference in HIV-infected pregnant women's attendance at follow-up medical visit amongst HIV-infected pregnant women who participated in a peer-mentoring program and an eight-session cognitive behavioral intervention compared to HIV-infected pregnant women who received standard care (RR 1.62, 95% CI 0.94-1.79) (Futterman 2010).

Findings of the 17 studies eligible for GRADE analysis

Overall, findings were a mixture of positive effects and no effects attributable to a range of community-based interventions.

<u>Home-based health assessment, education and support by community health workers</u>. Community-based interventions that included home-based health assessment, education and support by community health workers were shown to be associated with better levels of ART adherence in one of three studies (Kabore 2010), with viral suppression in one of three studies (Fatti 2012), and reduced mortality rates in two of four studies (Fatti 2012; Grimwood 2010).

<u>mHealth support intervention used by peer health workers at home visits</u>. Exposure to an mHealth-supported community-based intervention was shown to be associated with viral suppression at 96 weeks in one study (Chang 2010). However, no significant association between exposure to an mHealth intervention and virologic suppression were observed for earlier time points (Chang 2010; Chang 2011; Selke 2010). None of four studies of mHealth-supported interventions showed an association with ART adherence (Chang 2010; Chang 2011; Selke 2010; Simoni 2009). None of three mHealth studies that

examined mortality showed differences in mortality rates between intervention and control groups (Chang 2010; Chang 2011; Selke 2010).

Peer support interventions. One of three peer support interventions showed an association with better adherence (Taiwo 2010). One study of a peer support intervention that examined intervention effect on mortality showed no effect of the intervention on mortality (Taiwo 2010). One study that examined intervention effect on follow up appointments showed no effect (Futterman 2010).

Socioeconomic support. The one study of a socioeconomic support intervention showed reduction in mortality amongst participants exposed to the intervention (Talisuna-Alamo 2012).

Community Based DAART. Neither of two studies of community-based DAART showed an association with better adherence (Altice 2007; Pearson 2007). One study of community-based DAART that examined mortality did not show an intervention effect on mortality (Pearson 2007). However, one of two studies showed an association between receipt of DAART and reduced mean viral load (Macalino 2007). One study that examined the effect of community-based DAART on retention on 1st line ART regimen showed no effect of the intervention on this outcome (Altice 2007).

Quality of the evidence

Sixteen of the 17 studies amenable to GRADE analysis included adult populations, and one of the 17 included children (<10 years old) only. Therefore, the findings of this review may not be generalizable to populations of adolescents. Other concerns that must be addressed are the financial costs of community based strategies for improving health outcomes of HIV-infected populations, as well as consideration on how to optimize adherence to program protocols and quality of care provided by community health workers. There is also the potential for significant implementation challenges of scaling up community-based programs for supporting adherence when there is limited infrastructure for monitoring or supporting community health workers.

In the GRADE system, well-conducted randomized controlled trials (without additional limitations) provide high quality evidence, and observational studies without any special strengths (and without additional limitations) provide low-quality evidence. In this analysis, we found that the 10 RCTs provided low to very low quality evidence for the benefits of community based interventions and for most outcomes very low quality evidence due to the observational nature of the studies, the small number of events reported, and indirectness of the populations studied (i.e. adults, or children <10 years old).

Home-based health assessment, education and support by community health workers. Community-based interventions that included home-based health assessment, education and support by community health workers were shown to be associated with better levels of ART adherence in one of three studies (Kabore 2010), with viral suppression in one of three studies (Fatti 2012), and reduced mortality rates in two of four studies (Fatti 2012; Grimwood 2010). The quality of evidence is very low due to serious or very serious imprecision (few or very few events) and serious indirectness (studies did not include adolescents).

mHealth support intervention used by peer health workers at home visits. Exposure to an mHealth-supported community-based intervention was shown to be associated with viral suppression at 96 weeks in one study (Chang 2010). However, no significant association between exposure to an mHealth intervention and virologic suppression were observed for earlier time points (Chang 2010; Chang 2011; Selke 2010). None of four studies of mHealth-supported interventions showed an association with ART adherence (Chang 2010; Chang 2011; Selke 2010; Simoni 2009). None of three mHealth studies that examined mortality showed differences in mortality rates between intervention and control groups (Chang 2010; Chang 2011; Selke 2010). The quality of evidence is very low due to serious or very serious imprecision (few or very few events) and serious indirectness (studies did not include adolescents).

Peer support interventions. One of three peer support interventions showed an association with better adherence (Taiwo 2010). One study of a peer support intervention that examined intervention effect on mortality showed no effect of the intervention on mortality (Taiwo 2010). One study that examined intervention effect on follow up appointments showed no effect (Futterman 2010). The quality of evidence is very low due to serious or very serious imprecision (few or very few events) and serious indirectness (studies did not include adolescents).

Socioeconomic support. The one study of a socioeconomic support intervention showed reduction in mortality amongst participants exposed to the intervention (Talisuna-Alamo 2012). The estimates of effect are very uncertain from this study. The quality of evidence is very low due to very serious imprecision (very few events) and very serious indirectness (retrospective analysis of adult data) .

Community Based DAART. Neither of two studies of community-based DAART showed an association with better adherence (Altice 2007; Pearson 2007). One study of community-based DAART that examined mortality did not show an intervention effect on mortality (Pearson 2007). However, one of two studies showed an association between receipt of DAART and reduced mean viral load (Macalino 2007). One study that examined the effect of community-based DAART on retention on 1st line ART regimen showed no effect of the intervention on this outcome (Altice 2007). The quality of evidence is very low due to serious risk of bias in two studies, serious or very serious imprecision (few or very few events), and serious or very serious indirectness (studies did not include adolescents; two of the three studies were based in the United States).

Summary of the 10 studies not amenable to GRADE analysis

Ten studies were identified for inclusion in this review but presented insufficient information needed for GRADE analysis; they reported only odds ratios without numerators (Stubbs 2009), regression parameters (Igumbor 2011), had no comparator or the comparator was not the comparator of interest (i.e., standard care) (Achieng 2012; Bekker 2006; Chang 2009; Kipp 2010; Kipp 2011; Nglazi 2011; Nglazi 2012; Rich 2012; Stubbs 2009). Therefore, associations are briefly described below.

Mortality

One observational prospective cohort study of HIV-infected adolescents and adults (≥15 years) at a community-based ART clinic in South Africa reported probability of death in the first year of ART (7.9%, 95% CI 7.0% - 8.9%), and cumulative probability of death after 6 years (15.2%, 95% CI 13.1% - 17.6%)

(Nglazi 2011). Male sex, lower baseline CD4 cell count, and WHO stage III and IV were associated with higher mortality risk.

One observational study comparing HIV-infected adolescents (9-19 years) and young adults (20-28 years) at a public sector community-based ART program in South Africa reported similar overall mortality rates in adolescents (1.2 [95% CI 0.3-4.8] deaths per 100 person-years) and young adults (3.1 [95% CI 2.4-3.9] deaths per 100 person-years) (Nglazi 2012).

One observational retrospective cohort study conducted in Rwanda reported a low mortality rate (5%) at 2 years following ART initiation amongst HIV-infected adults in care at a community-based ART program (Rich 2012).

One non-randomized prospective cohort study conducted in Uganda compared treatment outcomes and mortality in rural community-based ART program with a hospital-based program in the same district (Kipp 2010). In this study, mortality at six months was not significantly different between both cohorts (11.9% vs. 9.0%).

Viral Failure or Viral Suppression

One observational study that evaluated outcomes of patients enrolled to a community-based, comprehensive ARV program staffed by peer health workers and nurses in Uganda reported 86% of active patients (211 or 246 tested) to have a viral load <400 copies/mL (Chang 2009). Virologic failure was significantly associated with lack of CD4 response and any history of prior ARV use. No external comparator was included in the study.

One observational retrospective cohort study of HIV-infected patients in government HIV treatment sites in South Africa showed that a significantly higher proportion of patients with a community-based adherence supporter had viral load <400 copies/mL at 6 months of treatment for a longer period compared to patients without a treatment supporter (Igumbor 2011). Also, a significantly greater proportion of patients in care at sites with community-based adherence supporter services maintained a suppressed viral load for a longer period compared to patients in care at clinics without a community-based adherence supporter service.

One observational prospective cohort study of HIV-infected adolescents and adults ($\geq$15 years) at a community-based ART clinic in South Africa reported high rates of virological suppression by 16 weeks after ART initiation, and to not vary significantly between successive years of recruitment (Nglazi 2011). Lack of virological suppression was associated with younger age (<25 years old), and high baseline viral load ($\geq$5 $\log_{10}$ copies/mL).

One observational study comparing HIV-infected adolescents (9-19 years) and young adults (20-28 years) at a public sector community-based ART program in South Africa reported adolescents to have significantly lower rates of virological suppression at 48 weeks compared to young adults (Nglazi 2012). In addition, adolescents had significantly higher risk of virological failure compared to young adults, though the association was not significant when comparing perinatally infected adolescents and young adults.

One observational retrospective cohort study conducted in Rwanda reported a high rate of virologic suppression at 2 years following ART initiation (97.5% with <500 copies/mL) amongst HIV-infected adults in care at a community-based ART program (Rich 2012).

One observational prospective cohort study conducted in South Africa reported high and sustained rates of virologic suppression (<400 copies/mL) over a 3-year period (100%, 92% and 98% for 2002, 2003, and 2004 cohorts) amongst HIV-infected adults in care at a public-sector community-based ART clinic (Bekker 2006).

One observational retrospective cohort study conducted in Kenya reported that time to treatment failure was significantly longer in patients who participated in peer support groups and/or home visits (Achieng 2012). Further, risk of treatment failure was significantly reduced amongst those who participated in support groups compared to patients who did not.

One non-randomized prospective cohort study conducted in Uganda reported that virologic suppression at six months was not significantly different between patients enrolled to a rural community-based ART program and patients in care at a hospital-based program in the same district (90.1% vs. 89.3%) (Kipp 2010). However, in a later report (Kipp 2011), the authors reported that a greater proportion of patients enrolled to the rural community-based ART program were more likely to achieve viral suppression at 2 years of follow up compared to patients in care at the hospital-based program.

ART Adherence

One observational retrospective cohort study of HIV-infected patients in care in government HIV treatment sites in South Africa showed that a significantly higher proportion of patients with a community-based adherence supporter attained a treatment pickup rate of over 95% compared to patients without a treatment supporter (Igumbor 2011).

One observational retrospective cohort study conducted in Mozambique reported that patients who had a treatment partner were significantly more likely to have higher levels of adherence compared to patients who had no treatment partner (Stubbs 2009). No differences in adherence were observed between patients with community-based treatment partners and patients with self-selected treatment partners.

One observational retrospective cohort study conducted in Kenya reported that a significantly greater proportion of patients who participated in support groups achieved higher mean adherence compared to patients who did not participate in support groups (Achieng 2012).

Retention in Care

One observational retrospective cohort study of HIV-infected patients in government HIV treatment sites in South Africa showed that the median retention time in care for patients in care at sites with community-based adherence supporter services was significantly greater than retention in care time of patients in care at clinics without a community-based adherence supporter service. (Igumbor 2011).

One observational retrospective cohort study conducted in Rwanda reported a high rate of retention in care two-years after ART initiation (92.3%) among HIV-infected adults in care at a community-based ART program (Rich 2012). In multivariate analysis, attrition was associated with older age (>50 years) and enrollment in 2006. An interaction existed between WHO clinical stage at baseline and sex. Among women, WHO clinical stage was not significantly associated with retention in care. However, men with WHO stage 3 or 4 disease at baseline were more likely to drop out of care compared to men with WHO stage 1 or 2 disease at baseline.

One observational prospective cohort study conducted in South Africa reported low rates of loss to follow up over a 3-year period (2.9%) amongst HIV-infected adults in care at a public-sector community-based ART clinic (Bekker 2006).

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