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Combined Effect of Co-trimoxazole Prophylaxis and Safe Water on Diarrhea amongst HIV-Exposed Infants and People Living with HIV/AIDS: A Systematic Review

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Abstract

Aim: Irrespective of co-trimoxazole prophylaxis, diarrhea among HIV-exposed infants (HEI) and people living with HIV and AIDS (PLWHA) remains unacceptably high. We aimed to determine the combined effect of improved water supply interventions and co-trimoxazole prophylaxis on frequency and severity of diarrhea among HEI and PLWHA. Methods: Using key search terms of safe sanitation, improved water supply, WaSH, co-trimoxazole prophylaxis, HIV-exposed, PLWHA, morbidity, mortality, diarrhea; we searched for published articles in PubMed, EMBASE, PsycINFO, AMED, CINAHL, DOAJ and Google Scholar databases guided by the acceptance practice developed by PROSPERO and COCHRANE. A PRISMA flow diagram was used to explain on the number of articles retrieved, retained, excluded and justifications for every action. A Mixed Method Appraisal Tool (MMAT) was used to assess the quality of the methodology of the selected studies. Results: Safe water and co-trimoxazole together reduced diarrhea episodes by up to 67% (IRR _ 0.33, 95% CI 0.24–0.46, P < 0.0001).

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The combined interventions resulted in 27% risk reduction in HIV disease progression whilst safe water alone was associated with reductions in the longitudinal prevalence of reported diarrhea of up to 53% among HEI aged ≤2 years (LPR = 0.47, 95% CI: 0.30–0.73, P < 0.001). Conclusion: The combined effect of co-trimoxazole and safe water was significantly higher than when each one of them were to be offered alone. An expanded WaSH response is critical to prevent diarrhea. Registration: CRD42021240512.

Keywords: Safe sanitation, improved water supply, WaSH, co-trimoxazole prophylaxis, HIV-exposed, PLWHA, morbidity, mortality, and diarrhea

Introduction

Excessive child diarrhea due to unsafe water in sub-Saharan Africa is a tragic but familiar story. Although access to safe water is a basic human need that ensures personal hygiene and restores human dignity (Luby, 2014), a significant proportion of HEI have no access to it (Makaudze, 2019). Many life-threatening opportunistic infections amongst HEI are caused by exposure to unsafe water, inadequate sanitation and poor hygiene (Daniels et al., 2019). The lack of safe water increases HEI‘s vulnerability to infectious enteric pathogens and gut enteropathy, which hinders the proper absorption of medicines and makes them less effective (Chandna et al., 2020). Safe water significantly reduces the odds of child diarrhoea by up to 45% (WHO, 2014). Many studies (Makaudze, 2019; Daniels et al., 2019; Kamuhabwa and Manyanga, 2015), point to the fact that basic sanitation is key for child survival. Whilst there is evidence that high quality sanitation affect child health outcomes, there is no implementable roadmap to harness benefits achievable by an integration of safe water into HIV treatment, care and support services.

The population of HEI is expanding, and reached nearly 15 million in 2017 (Chandna et al., 2020). Co-trimoxazole is one of the main biomedical interventions recommended by World Health Organization (WHO) in the management of HEI. It contains two antibiotics: sulfamethoxazole and trimethoprim. Trimethoprim and sulfamethoxazole have enhanced effect when used concomitantly. This is because they inhibit sequential stages in the folate synthesis pathway of the microorganisms. It is commonly abbreviated in the following ways: SXT, TMP-SMX, TMP-SMZ or TMP-Sulfa.

To reduce the risk of HIV-associated opportunistic infections, WHO recommends that infants exposed to HIV through breastfeeding receive co-trimoxazole prophylaxis from 6 weeks of age until an age-appropriate HIV test can be used to ascertain the child’s infection status after cessation of breastfeeding. Co-trimoxazole is associated with a 36% reduction in respiratory morbidity and a 41% reduction in diarrhoeal morbidity (Davis et

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al, 2017). This systematic review was carried out to gather and synthesize evidence on the effectiveness of integrating safe water and co-trimoxazole preventive therapy in reducing morbidity and mortality among HEI.

The question that this systematic review tries to resolve is: What is the combined effect of improved water supply interventions and co-trimoxazole preventive therapy on frequency and severity of diarrhea among HEI and PLWHA? Is the value and performance of two approaches combined much greater than the sum of the separate individual efforts? The target main outcome of the review was diarrhoea among HEI and PLWHA.

Methods

Protocol

This systematic review followed guidelines developed by the PROSPERO for systematic search and selection. PROSPERO is an international database for registering systematic reviews in various professions including the health sector (Page et al., 2018). The protocol was published in the PROSPERO database with registration number CRD42021240512. Details about the protocol have been published elsewhere (https://www.crd.york.ac.uk/prospero/#myprospero). PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram was used to show the number of articles retrieved, retained, excluded with justifications rendered for every action. A PRISMA is a set of items founded on research evidence that improves and supports the reporting clarity of the systematic reviews and meta-analyses (Moher et al., 2009). A Mixed Method Appraisal Tool (MMAT) was used to appraise the quality of the studies included.

Inclusion criteria

Eligible studies fulfilled the following criteria: studies involving morbidity and mortality of PLWHA and HEI; studies aimed at identifying independent and combined effects of co-trimoxazole and safe water supply on frequency and severity of diarrhea among HEI and PLWHA.

Exclusion criteria

Articles were excluded from this systematic review if they were: (1) reviews, perspectives, communications and (2) written in languages other than English.

Information source /search strategy

The following seven database sources were used to gather the required research articles; PubMed, EMBASE, PsycINFO, AMED, CINAHL, DOAJ and Google Scholar. MeSH database search in PubMed was conducted to

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

identify search terms and keywords. These keywords combined with Boolean operations OR and AND were used to search and retrieve articles from the databases. The search period for the research articles in the mentioned databases started from February 2002 to February 2022 covering a period of 20 years. The following key search words/terms were used; safe sanitation AND/OR improved water supply AND/OR WaSH AND/OR co-trimoxazole prophylaxis AND/OR HIV-exposed AND/OR PLWHA AND/OR morbidity AND/OR mortality AND/OR diarrhea.

Efforts were made to identify both published and unpublished interventional studies by manually checking the reference list of the articles that met the inclusion criteria. Hand searching of the key journals was also done. Thereafter, identified studies were checked to determine their eligibility. See Table 1 below.

Table 1. Search strategy

Databases	Search	Search word/terms	Results
PubMed	Title and abstract	safe sanitation AND/OR improved water supply AND/OR WaSH AND/OR co-trimoxazole prophylaxis AND/OR HIV-exposed AND/OR PLWHA AND/OR morbidity AND/OR mortality AND/OR diarrhea	1
EMBASE	Title, abstract and full article	safe sanitation AND/OR improved water supply AND/OR WaSH AND/OR co-trimoxazole prophylaxis AND/OR HIV-exposed AND/OR PLWHA AND/OR morbidity AND/OR mortality AND/OR diarrhea	0
PsycINFO	Title, abstract and full article	safe sanitation AND/OR improved water supply AND/OR WaSH AND/OR co-trimoxazole prophylaxis AND/OR HIV-exposed AND/OR PLWHA AND/OR morbidity AND/OR mortality AND/OR diarrhea	1

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

AMED	Title and abstract	safe sanitation AND/OR improved water supply AND/OR WaSH AND/OR co-trimoxazole prophylaxis AND/OR HIV-exposed AND/OR PLWHA AND/OR morbidity AND/OR mortality AND/OR diarrhea		0
CINAHL	Title and abstract	safe sanitation AND/OR improved water supply AND/OR WaSH AND/OR co-trimoxazole prophylaxis AND/OR HIV-exposed AND/OR PLWHA AND/OR morbidity AND/OR mortality AND/OR diarrhea		0
DOAJ	Title, abstract and full article	safe sanitation AND/OR improved water supply AND/OR WaSH AND/OR co-trimoxazole prophylaxis AND/OR HIV-exposed AND/OR PLWHA AND/OR morbidity AND/OR mortality AND/OR diarrhea		0
Google Scholar	Title, abstract and full article	safe sanitation AND/OR improved water supply AND/OR WaSH AND/OR co-trimoxazole prophylaxis AND/OR HIV-exposed AND/OR PLWHA AND/OR morbidity AND/OR mortality AND/OR diarrhea	6	
Reference search from other sources	Title, abstract and full article	safe sanitation AND/OR improved water supply AND/OR WaSH AND/OR co-trimoxazole prophylaxis AND/OR HIV-exposed AND/OR PLWHA AND/OR morbidity AND/OR mortality AND/OR diarrhea		0
	Total Result Search			8

Study selection

Articles identified from the databases were imported to Mendeley Reference Management Software. Thereafter, the title, abstract and finally full articles were reviewed against the set inclusion criteria.

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

Data collection process

The process of data extraction started with a database search of relevant articles as described above and following the PRISMA guidelines (see Figure 1). Titles and/or abstracts of studies were retrieved and studies that potentially met the inclusion criteria as outlined above were identified. The full texts of potentially eligible studies were retrieved and independently assessed for eligibility by two authors. The inconsistencies between the two authors (EC & BM) over the eligibility of some studies were discussed and resolved with a third author (WS) or (RC). A table was used to extract data from the studies included for assessment of study quality and synthesis evidence. The details included; author, year of study, type of participants, age, setting, country, sample size, study design and methods, study purpose/objectives, study outcomes and results. All relevant information was extracted from each study, summarized and documented.

Search outcome

An initial search of the databases and other sources yielded 1055 articles. Only 321 articles were left after removal of duplicates. The remaining articles were further filtered and 292 articles were excluded because they were either abstracts only or they contained a totally different study topic. All full-text articles were further assessed for eligibility and 21 articles were dropped because they lacked sufficient details for the intended study. The remaining 8 articles were selected for the final analysis (see Figure 1).

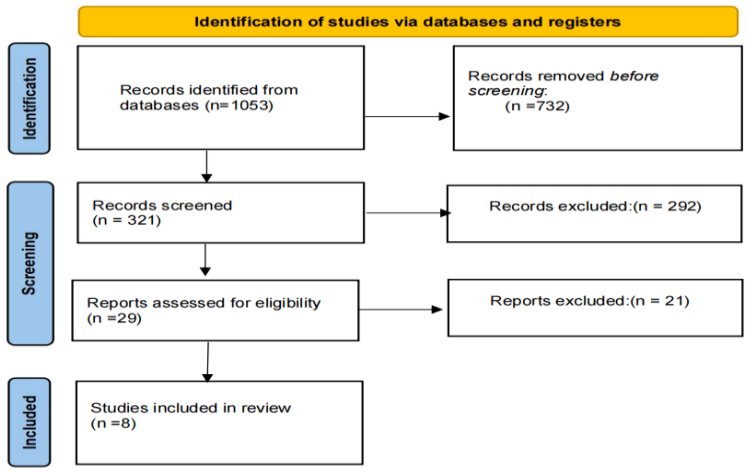

Figure 1.The PRISMA Flow diagra

Data synthesis

The authors provided a narrative synthesis of the findings from the included studies. Emphasis was on the morbidity and mortality among HIV exposed infants and PLWHA. A subset analysis was categorized based on the

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

set study outcomes, thus; morbidity and mortality. A narrative synthesis was then conducted on the included articles.

We reviewed studies that reported the effect of improved water supply interventions and co-trimoxazole prophylaxis on child diarrhea. A total of eight (8) studies were selected and are summarized in Table 2 below.

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

Table 2. Summary of studies

Author	Participants	Age	Setting	Country	Sampsize	Study design	Study purpose/ Objective	Outcomes	Results
Prendergast et al 2018	HEI HIV unexposed PLWHA Unknown status	Children and adults	community	Zimbabwe	1394	Cluster RCT	To test the effect of IYCF and safe water, on linear growth and haemoglobin concentrations.	Inconsistent reductions in diarrhoea	9 (2%) of 370 children in the WASH groups were stunted and wasted compared to 6 (2%) of 291 in the non-WASH groups (absolute difference 0%; 95% CI −2 to 3)
Rachel Paletz (Paletz et al 2012)	HIV exposed infants and Non exposed infants	< 2 years	Household	Chongwe district, Zambia	1138	Cluster RCT	To assess beneficial effects water filtration and safe storage in households caring for HIV exposed infants	Reduced diarrhea	Safe water was associated with reductions in the longitudinal prevalence of reported diarrhea of 53% among children (LPR = 0.47, 95% CI: 0.30–0.73, p = 0.001) and 54% among all household members (LPR = 0.46, 95% CI: 0.30–0.70,p,0.001).

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

Ezra J. Barzilay (Barzilay et al 2011	HIV infected women	Not indicated	Household	Lagos, Nigeria	187	RCT	To evaluate the impact of point of use water quality interventions	Reduced diarrhea	Significant diarrhea reduction amongst persons who did not take Cotrimoxazole prophylaxis (-62%, p=0.02) Point of use water treatment was associated with a reduced risk of diarrhea in PLWHA Regular water treatment was required to achieve health benefits
Jiayin Xue (Jiayin Xue et al 2010)	Mothers to HIV exposed infants	Women of childbearing age	Household	Lilongwe, Malawi	474	Prospective observational study	To evaluate a pilot prevention of mother-to-child transmission post-natal programme in Lilongwe, Malawi, through observed retention and infant diarrhoeal rates.	Reduced diarrhea	The infant diarrhoeal rate was low, suggesting benefits of regular medical care with hygiene package usage Seventeen of 357 (4.8%, 95% CI 2.8–7.5%) of the infants and 3 (0.8%, 95% CI 0.2–2.4%) of the mothers were reported to have had at least one episode of diarrhoea

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

Ram K. Shrestha (Shrestha et al 2006)	PLWHA HIV affected households	Unspecified age groups	Homebased care	Rural part of Uganda	196	RCT	To evaluate the cost and cost-effectiveness of safe water supply intervention for HIV affected households	Reduced diarrhea	Safe water averted 37 diarrhea episodes and 310 diarrhea days and gained 0.155 DALYs for the entire household per 100 person-years of participation by HIV-affected households No mortality benefit was reported
John R. Lule **Lule et al 2005**	PLWHA HIV negative household members	Unspecified age group	Household	Rural part of Uganda	2030	RCT	To evaluate safe water intervention on the incidence and severity of diarrhea among persons living with HIV	Reduced diarrhea	Safe water was equally effective with or without cotrimoxazole preventive therapy In combination they reduced diarrhea episodes by 67% (IRR _ 0.33, 95% CI _ 0.24–0.46, P < 0.0001), days with diarrhea (5.5 versus 10.5 days per person-years; IRR_0.46, 95% CI_0.32–0.66, P < 0.0001), and days of work or school lost due to diarrhea (2.9 versus 5.1 days per person-years; IRR _ 0.53, 95% CI 0.34–0.83, P _ 0.0056)

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

O Reilly et al., 2014	PLWHA and households	>18 years	Household	Amhara, Ethiopia	749	RCT	To evaluate effectiveness of preventive health interventions for PLWHA	Reduced diarrhea	Intervention group clients were less likely than comparison clients to report illness from any cause (44% vs. 67%, $p<0.05$) and fewer health facility visits for diarhoea (4% vs. 7%, $p=0.11$) than comparison clients.
Judd L. Walson (Walson et al 2013)	PLWHA	Adults	HIV care site	Kenya	589	RCT	To determine whether the use of long lasting insecticide treated bed nets and point of use water filters can delay HIV disease progression	Reduced diarrhea	Incidence of malaria and diarrhea were significantly lower in the intervention group The combined interventions of insecticide treated bed nets, safe water resulted in 27% risk reduction in HIV disease progression, and a 24% decrease in cd4 cell count decline among already receiving cotrimoxazole propbylaxis

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

Results

Quality appraisal

The methodological quality of included studies was critically appraised using the Mixed Method Appraisal Tool (MMAT). Based on the MMAT, three studies scored 100%; all of which where randomized controlled trials. The other four studies scored (80%) each. Only one study scored 60%. Among these, one study used a non-blinded design. Another study had possible confounders in the research design and the third one had incomplete outcome data. Randomization of one study was unclear, hence the 80% score. The study whose methodology scored 60% had inappropriate subject selection criteria with unclear research hypothesis. Nonetheless, all the nine studies were categorized as high quality after meeting almost all core criteria for their study design. The overall quality cut-off point was set at 60%. With an average score of 85% across the evaluated articles, the studies were categorized as very high quality. Therefore, the findings from our systematic review can be relied upon to inform policy, practice, education and research. See Table 3 below.

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

Table 3. Mixed Method Appraisal Tool (MMAT)

Name of study author	Type of study	Methodological quality criteria	Y/N	Comments	Score
Prendergast et al 2018 Independent and combined effects of improved water, sanitation, and hygiene, and improved complementary feeding, on stunting and anaemia among HIV-exposed children in rural Zimbabwe: a cluster-randomisedcontrolled trial	Randomized controlled trial	2.1. Is randomization appropriately performed? 2.2. Are the groups comparable at baseline? 2.3. Are there complete outcome data? 2.4. Are outcome assessors blinded to the intervention provided? 2.5 Did the participants adhere to the assigned intervention?	N N Y Y Y	Inappropriate subject selection criteria with unclear research hypothesis	60%
Paletz et al 2012 Assessing Water Filtration and Safe Storage in Households with Young Children of HIV-Positive Mothers: A Randomized, Controlled Trial in Zambia	Randomized controlled trial	2.1. Is randomization appropriately performed? 2.2. Are the groups comparable at baseline? 2.3. Are there complete outcome data? 2.4. Are outcome assessors blinded to the intervention provided? 2.5 Did the participants adhere to the assigned intervention?	Y Y Y N Y	A non-blinded design was used because previous attempts to blind the same intervention were unsuccessful; this can be a potential source of bias	80%

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

Barzilay et al 2011 Diarrhea prevention in people living with HIV: an evaluation of point of use water quality intervention in Lagos, Nigeria	Quantitative Non randomized study	3.1. Are the participants representative of the target population? 3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)? 3.3. Are there complete outcome data? 3.4. Are the confounders accounted for in the design and analysis? 3.5. During the study period, is the intervention administered (or exposure occurred) as intended?	Y Y Y N Y	Interpretation of a pre/post intervention study may be misleading, since changes in the outcome my be a reflection of the effect of the intervention or just a natural course of the the disease	80%

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

Xue et al 2010 Use of nutritional and water hygiene packages for diarrhoeal prevention among HIV-exposed infants in Lilongwe, Malawi: an evaluation of a pilot prevention of mother-to-child transmission post-natal care service	Quantitative Non randomized study	3.1. Are the participants representative of the target population? 3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)? 3.3. Are there complete outcome data? 3.4. Are the confounders accounted for in the design and analysis? 3.5. During the study period, is the intervention administered (or exposure occurred) as intended?	Y Y Y N Y	Women were enrolled at different times between October and March, and follow-up visits span into July, these months encompass both the dry and wet seasons, introducing more variability	80%

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

Shrestha et al 2006 Cost-effectiveness of home-based chlorination and safe water storage in reducing diarrhea among HIV affected households in rural Uganda	Randomized controlled trial	2.1. Is randomization appropriately performed?	Y	100%
		2.2. Are the groups comparable at baseline?	Y	
		2.3. Are there complete outcome data?	Y	
		2.4. Are outcome assessors blinded to the intervention provided?	Y	
		2.5 Did the participants adhere to the assigned intervention?	Y	
Lule et al 2005 Effect of home-based water chlorination and safe storage on diarhoea among persons with human immunodeficiency virus in Uganda	Randomized controlled trial	2.1. Is randomization appropriately performed?	Y	100%
		2.2. Are the groups comparable at baseline?	Y	
		2.3. Are there complete outcome data?	Y	
		2.4. Are outcome assessors blinded to the intervention provided?	Y	
		2.5 Did the participants adhere to the assigned intervention?	Y	

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

O Reilly et al 2014 Improved health among people living with HIV/AIDS who received packages of proven preventive health interventions, Amhara, Ethiopia	Randomized controlled trial	2.1. Is randomization appropriately performed? 2.2. Are the groups comparable at baseline? 2.3. Are there complete outcome data? 2.4. Are outcome assessors blinded to the intervention provided? 2.5 Did the participants adhere to the assigned intervention?	N Y Y Y Y	Not clear	80%
Walson et al 2013 Evaluation of impact of long-lasting insecticide-treated bed nets and point-of-use water filters on HIV-1 disease progression in Kenya	Randomized controlled trial	2.1. Is randomization appropriately performed? 2.2. Are the groups comparable at baseline? 2.3. Are there complete outcome data? 2.4. Are outcome assessors blinded to the intervention provided? 2.5 Did the participants adhere to the assigned intervention?	Y Y Y Y Y		100%

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

Study characteristics

Eight (8) studies fulfilled the eligibility criteria. These studies were conducted in Nigeria (Barzilay et al., 2011), Kenya (Walson et al 2013), Ethiopia (O Reilly et al., 2014), Malawi (Xue et al., 2010), Zambia (Paletz et al., 2012), Zimbabwe (Prendergast et al., 2018) and two studies came from Uganda (Shrestha et al 2006 and Lule et al., 2005). Refer to Table 2. Seven (7) studies were quantitative randomized controlled trials whilst the other one (1) was simply quantitative non-randomized controlled trial. One (1) study enrolled HIV positive women attending PMTCT and their HEI (Xue et al., 2010) while two (2) other studies focused on children living with HIV (Walson et al 2013; Prendergast et al., 2018). Five (5) studies focused on children living with HIV and their households (Barzilay et al., 2010; Shrestha et al., 2006; Peletz et al., 2012; Lule et al., 2005; O Reilly et al., 2014). One (1) study (Prendergast et al., 2018) focused on HIV positive pregnant and breastfeeding women, HEI, HUEI (HIV-unexposed infants) and children whose HIV status was not ascertained at time of enrollment into the study. Nonetheless, all populations of interest in this study were taking co-trimoxazole prophylaxis as per recommended protocols.

Summary of the findings

Studies included in this review were analyzed based on the main outcome of interest- diarrhea amongst HEI and PLWHA receiving co-trimoxazole. The presentation and interpretation of the results follow these categories as narrated below.

Morbidity

All the eight studies reported diarrhea as either their primary or secondary outcome. Besides diarrhea, the other effects of morbidity were expressed through reduction in HIV disease progression (Walson et al., 2013) and Daily Adjusted Life Years (DALY) (Shrestha et al., 2006). According to Walson et al., 2013 study, the incidence of clinically diagnosed malaria within the previous 3 months was significantly lower in the intervention group than in the control group (RR 0.66; 95% CI 0.49–0.88). The study further reported that combined interventions resulted in 27% risk reduction in HIV disease progression, and a 24% decrease in CD4+ cell count decline among those already receiving co-trimoxazole. Gains of 0.155 DALYs for the entire household per 100 person-years of participation by HIV-affected households was reported in one study by Shrestha et al., (2006). Therefore, using safe water had extended health benefits to other members of the households who were not infected with HIV. In another study, in Amhara- Ethiopia, (O Reilly et al., 2014) PLWHA who had access to safe water combined with co-trimoxazole were less likely to report illness from any cause (44% vs. 67%,

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

P<0.05) than comparison clients. The combination of safe water was protective against other opportunistic infections which led to fewer health facility visits for opportunistic infections.

Mortality

One study with mortality as an outcome met the inclusion criteria. The study sought to assess water filtration and safe storage in households with young children of HIV-positive mothers: In this randomized controlled study conducted in Zambia, Peletz et al., (2012) reported nine (9) deaths, all in children <2 years; 3/61 (5%) in the intervention arm and 6/60 (10%) in the control group. In the intervention group, only one (1) death was due to diarrhea; other deaths resulted from organophosphate poisoning. In the control group, deaths were potentially all due to diarrhea. All but one (1) was HIV-exposed and two children were known to be HIV-positive. There was no evidence of an impact of the intervention on all-cause mortality among children <2 years (RR = 0.56; 95% CI: 0.13–2.37, P= 0.43). Another study (O Reilly et al., 2014) reported eight (8) deaths (three (3) in the intervention group and five (5) in the control group). The three (3) deaths in the intervention group occurred due to suicide and pneumonia. A diarrheal death was just one from the control group. Other deaths were from unrelated causes. Overall, the quality of evidence of studies examining mortality was determined to be poor due to the limited number of studies that reported mortality as the major outcome.

Safe water

A study from Uganda on the effect of home-based water chlorination and safe storage on diarrhea among PLWHA taking co-trimoxazole (Lule et al., 2005) revealed that each diarrhea episode was associated with a 0.12 log10 copies/mL per-year increase in viral load (95% CI_ 0.01–0.23, *P* _0.037). The HIV viral load increased by 0.40 log10 per person year for persons with HIV using safe water compared with 0.71log10 per person-year for those not using safe water.

A randomized controlled trial of HEI and their households in Zambia (Peletz et al., 2012) reported significant reductions in the longitudinal prevalence of diarrhea of 53% among HEI (LPR = 0.47, 95% CI: 0.30–0.73, P < 0.001) and 54% among all household members (LPR = 0.46, 95% CI: 0.30–0.70, P<0.001). The study aimed to evaluate benefits of safe water for households caring for HEI.

In a randomized controlled trial among people with HIV in rural Uganda (Shrestha, 2006), the household-level provision of safe water was found to reduce the frequency of diarrhea episodes by 25%, days with diarrhea by 33%, and the frequency of dysentery by 28%. SWS was similarly effective

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

whether people with HIV were taking co-trimoxazole, which is recommended for reducing morbidity and mortality among PLWHA.

The results of a randomized controlled trial (Walson et al., 2013) suggest that the addition of an long lasting insecticide bednets (LLIN) and a point-of-use water filtration device to the existing package of care delayed HIV-1 disease progression resulting in a 27% risk reduction in HIV disease progression and a 24% decrease in CD4+ cell count decline among HIV-1-infected adults already receiving co-trimoxazole.

A Malawian study (Xue et al., 2010), suggests that effective hygiene education and improved water supply and sanitation are critical for both the HIV infected mothers and infants who are at risk of opportunistic infections. In this study, safe water led to lowered diarrheal rates in HEI before and after weaning, although safe water alone was not sufficient to reduce diarrhea during the weaning period.

An evaluation study (Barzilay et al., 2010) of point of use water quality intervention in Lagos, Nigeria among PLWHA found that the percentage changes in diarrhea rates between baseline and post intervention surveillance periods was statistically significant among non-users of co-trimoxazole (-62%, P=0.02) and among persons who used neither co-trimoxazole nor Antiretroviral treatment (-46%, P=0.02). Safe water was associated with a significant reduction in diarrhea and regular water treatment was required to achieve health benefits.

The impact of co-trimoxazole and safe water produced overwhelming benefits of integration leading to the adoption of expanded early co-trimoxazole and safe water usage among HEI and PLWHA in Zambia. Basic health care packages that included Wuha Agar water treatment solution, safe water storage vessels, soap, condoms and co-trimoxazole proved to be an effective remedy for the reduction in diarrhea rates and improving health outcomes in a study that aimed to assess whether basic preventive health interventions have an impact on PLWHA in Amhara, Ethiopia. In this study, (O'Reilly et al., 2014) intervention clients were less likely than comparison clients to report illness (44% vs. 67%, P<0.001) or health facility visits for illness (74% vs. 95%, P<0.001), and had lower median illness scores (1.0 vs. 3.0, P<0.05).

A cluster randomized controlled trial in Zimbabwe failed to establish consistent interactions between WaSH interventions and HIV positive mothers and their exposed infants taking co-trimoxazole. Although the elementary WaSH intervention had no effect on child growth, the intervention group significantly reduced a 7-day prevalence of diarrhea at the 18- month visit: 17 (8%) of 209 children in the non-WaSH groups had diarrhea, compared with 10 (3%) of 290 in the WaSH groups (absolute difference 5% CI 0-9); RR 0.42,

 ISSN: 1857-7881 (Print) e - ISSN 1857-7431

95% CI 0.21-0.85), but had no effect at 12 months or on other measures of morbidity.

Put in general terms, high safe water alone was equally effective with or without co-trimoxazole. The protective effects of WaSH ranged from 53% among HIV-exposed infants aged ≤2 years and 54% among non-infected household members.

Co-trimoxazole prophylaxis

Three studies outlined detailed performance of co-trimoxazole for PLWHA (Prendergast et al., 2018; Walson et al., 2013; Lule et al., 2005). A study evaluating the impact of long-lasting insecticide-treated bed nets and point-of-use water filters on HIV-1 disease progression in Kenya (Walson et al., 2005), reported significant difference in time to CD4+ cell count of less than 350 cells/ml (hazard ratio 0.73; 95% CI 0.57–0.95). Individuals in the intervention cohort had a lower risk of reaching a CD4+ cell count of 350 cells/ml or less compared with participants in the control cohort.

The CHAP trial in Zambia (2001-2003) demonstrated that daily co-trimoxazole reduced morbidity and mortality among HIV-infected children in sub-Saharan Africa. Data from this trial, showed that co-trimoxazole use in untreated HIV-infected children was associated with slower decreases in weight- and height-for-age and improvements in anemia. Mean annual change in CD4 cell percentage was 10.14% (95% confidence interval [CI], 2.55 to .83) for the co-trimoxazole group and -0.37% (95% CI, 21.18 to .44) for the control group. Compared with children randomized to receive placebo, children randomized to receive co-trimoxazole had slower decreases in weight-for-age (P=0.04) and height-for-age (P=0.01), and greater increase in hemoglobin level (P=0.01). The effects of co-trimoxazole on growth was primarily attributable to a reduction in diarrhea and other severe infections among children receiving the prophylaxis.

A Ugandan study (Lule et al., 2005) sought to understand the effect of home-based water chlorination and safe storage on diarrhea among PLWHA. In this study, co-trimoxazole was associated with fewer diarrhea episodes: (0.9 versus 2.0 episodes per person-year; IRR _ 0.42, 95% CI _ 0.34–0.51, P < 0.0001), days with diarrhea (7.1 versus 10.1 days per person- years; IRR _ 0.64, 95% CI _ 0.50–0.83, P=0.0006), and days of work or school lost due to diarrhea (3.6 versus 5.1 days per person-years; IRR _ 0.65, 95% CI _ 0.46–0.92, P=0.0142). The SWS and cotrimoxazole together reduced diarrhea episodes by 67%: (IRR _ 0.33, 95% CI _ 0.24–0.46, P < 0.0001), days with diarrhea (5.5 versus 10.5 days per person-years; IRR_0.46, 95% CI_0.32–0.66, P < 0.0001), and days of work or school lost due to diarrhea (2.9 versus 5.1 days per person-years; IRR _ 0.53, 95% CI _ 0.34–0.83, P= 0.0056) compared with no intervention).

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Co-trimoxazole is traditionally associated with a 41% reduction in diarrhoeal morbidity (Davis et al, 2017). In this systematic review, co-trimoxazole whilst offered together with WaSH was associated with a reduction in diarrhea ranging from to 53% to 67%.

Discussion

Infants younger than 12-months and infants with HIV have compromised immune systems and are more at risk for bacterial and parasitic infections resulting from unsafe water supply. Evidence from the eight studies that we included in this systematic review reported on diarrhoea as an outcome. The studies suggest that safe water has added protective effects against morbidity for persons who take prophylactic antibiotics for opportunistic infections. Notably, one study (Xue et al., 2010) observed that point-of use water treatment and hygiene education were associated with lowered diarrheal rates in HEI before and after weaning. This is a positive assertion of the complementarity of safe water (a non-biomedical intervention) and other existing biomedical interventions for HEI. A study in Zambia (Peletz et al., 2012), found that water filtration and safe water storage led to significant reductions in the longitudinal prevalence of diarrhea among HEI and their family members too. This extended benefit provides convenient home-based care practices and minimizes person to person transmission of diarrhea-causing pathogens within HIV affected family members.

Despite this evidence, results from other studies (Prendergast et al., 2018; O'Reilly et al., 2014; Walson et al., 2013; Barzilay et al., 2010; Shrestha, 2006; Lule et al., 2005) focused on co-trimoxazole typically for PLWHA in general. Reduction in HIV disease progression was reported in only one prospective observational study (Walson et al., 2013) of combined effects of long lasting insecticide treated bed nets and point-of-use water filtration. The combined intervention resulted in risk reduction in HIV disease progression.

Interestingly, the safe water intervention study in Zimbabwe on HEI (Prendergast et al., 2019) did not establish a consistent effect on diarrhea. It was hypothesized that safe water and WaSH in general would reduce diarrhea and prevent enteric dysfunction which would in turn, reduce stunting. Although uptake of the WaSH intervention was well implemented, it did not stimulate household behaviors within the limited and specified study period. Secondly, the study had complexities in the initial enrollment of research participants as they ranged from HEI, HEUI and HIV-unexposed (HIV negative) infants and those that had uncertain HIV status. Other research participants included pregnant and breastfeeding mothers and the specific sample size for HEI was not clear. It is highly likely that the null effect of the WaSH intervention was due to insufficient power to detect an effect. Again,

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we reasoned that group sizes were vastly unequal with violation of homogeneity of variance then a possible underestimation of the significance level would ensue resulting in false rejection of the null hypothesis.

Limitations of the study

All the included studies used self-reported diarrhea rates as the outcome, which may be prone to bias and recall-errors. Some studies were funded by water treatment products manufacturers, which raised the possibility of conflict of interest. It was further observed that researching safe water interventions alongside other multiple HIV preventive services that benefit PLWHA such as long lasting insecticidal mosquito nets (LLINs), nutrition/ food supplements, and Infant and Young Child Feeding (IYCF) programs without a study design that allows researchers to separate the impacts could result in misleading conclusions.

Implications of the study findings for practice, research and policy

The United States President's Emergency Plan For AIDS Relief (PEPFAR) is a United States government initiative that facilitates direct support and the delivery of HIV prevention, care and treatment services to help those suffering from the disease. Irrespective of the funding of HIV programs under the PEPFAR, there is persistent diarrhea experienced by HEI and PLWHA linked to poor WaSH. This translates to loss of funds that threatens the intended goal (Garriga and Foguet, 2013). One of the key PEPFAR objectives is to reduce morbidity and mortality among PLWHA. While it is necessary to identify interventions targeted at the primary causes of HIV-related illnesses, using co-trimoxazole as prevention; how often are such preventive drugs washed down and lost through diarrhea as a result of drinking contaminated water and poor WaSH practices?

Integrating and leveraging resources among partner organizations could enhance maximization and the most efficient use of funds, personnel and other resources within the WaSH and HIV sector. For every $1 invested in water and sanitation WHO estimates a $4 economic return and a 1.5% gain of global gross domestic product (GDP) through reduced health costs, workplace productivity and fewer premature deaths. This results in $18.5 billion in economic benefits each year from prevented diarrhea (WHO, 2014).

As it stands, there is no implementable roadmap to harness the benefits achievable by WaSH/HIV/AIDS integration. As such, there is need to develop a comprehensive WaSH/HIV/AIDS response strategy that addresses particular needs of HEI, PLWHA and their families. As an expanded response to address exposed infants' vulnerability to HIV/AIDS, household water treatment (HHWT) and point of use water treatment must be scaled up particularly

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where there is no other safer source of drinking water available for PLWHA and their families.

Conclusion

Co-trimoxazole whilst offered together with safe water was associated with a reduction in diarrhea. The combined effect was significantly higher than when each one of them were to be offered alone. This evidence supports that WaSH programming carries incremental value for HEI and PLWHA. Mortality, another thematic outcome of interest within this systematic review lacked sufficient data to generate firm conclusions. An expanded WaSH response in fighting HIV amongst infants is important to prevent multiple opportunistic infections that can accelerate mother to child transmission of the virus and rapid disease progression.

Conflict of interest: The authors declare no competing interests.

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