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The Impact of HIV Care and Support Interventions on Key Outcomes in Low and Middle-Income Countries: A Literature Review. Introduction

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Background

As of December 2012, an estimated 35.3 million persons were living with HIV; approximately two thirds of these people were living in sub-Saharan Africa.[1] The response to the HIV pandemic in Africa and in other low-and middle-income regions of the world has consisted of a variety of bilateral and multi-lateral support from donor agencies, as well as local support from countries that have been able to afford it. A majority of the support has been directed towards HIV care and treatment.

Accordingly, the past ten years have witnessed a remarkable increase in the number of HIV-infected persons receiving antiretroviral therapy (ART) in low- and middle-income countries--from 300,000 in 2003 to 9.7 million in 2012[1,2]. Expanded access to ART in these countries has led to significant proportions of eligible persons enrolled on ART, reaching coverage rates as high as 61% based on the World Health Organization (WHO) treatment guidelines eligibility criteria of CD4 <350 cells/uL) in 2012.[1] In 2013, WHO revised its guidelines to indicate eligibility at CD4 <500 cells/uL; under these criteria, only 34% of eligible persons were on ART in 2013.[1] Nevertheless, these changes in access to ART were estimated to have averted 4.2 million deaths through 2012[2].[1]

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Disclaimer: The findings and conclusions in this article are those of the authors and should not be construed to represent the positions of the U.S. Department of State's Office of the U.S. Global AIDS Coordinator, the U.S. Centers for Disease Control and Prevention, the U.S. Agency for International Development, the U.S. Department of Defense, or the U.S. Federal Government.

HIV treatment programs in low- and middle-income countries have been supported by a variety of sources, including over $50 billion through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) from 2004 to 2013[3]. PEPFAR programs are coordinated by the U.S. Department of State's Office of the U.S. Global AIDS Coordinator (OGAC) in Washington, D.C.,; oversight of in-country expenditures is supported by additional U.S. government(USG) agencies with the majority of funds concentrated in 36 countries and regions 4 in sub-Saharan Africa, South and Central Asia, Eastern Europe, Central America and the Caribbean. PEPFAR supports a range of HIV care and treatment services besides ART including clinical (e.g. monitoring to determine eligibility for ART and prevention and treatment of opportunistic infections) and non-clinical services (e.g. psychological, social, and preventive)[4]. Services implemented through PEPFAR support in each country are determined through a dialogue between the USG, and host governments. PEPFAR country operating plans and budgets are submitted annually and reviewed by USG staff.

In 2013, the U.S. Institute of Medicine (IOM), in its evaluation of PEPFAR, called attention to the wide range of non-ART care and support services supported by PEPFAR, and challenged PEPFAR to assess the impact of these services on key outcomes. The IOM recommended a prioritization of services that should be funded in PEPFAR country portfolios[5] (IOM, 2013). In response, the PEPFAR Adult Care and Support interagency technical working group (TWG) reviewed available evidence on the impact of non-ART adult care and support interventions on key outcomes to assist PEPFAR country teams as they make care and support program decisions. This paper presents the general approach and methods used in these reviews.

METHODS

In late 2013, the PEPFAR Adult Care and Support interagency TWG undertook a review of the literature on each of 12 non-ART adult care and support services commonly funded by PEPFAR to evaluate the impact of each intervention on five outcomes: mortality, morbidity, retention in HIV care, quality of life, and prevention of ongoing HIV transmission. A 13th intervention—tuberculosis (TB) screening and treatment--was not reviewed due to the abundance of information on this intervention and its recognized importance (and separate budget allocations) in PEPFAR programming. A list of the 13 care and support interventions (including TB screening and treatment) is shown in Table 1.

Review teams

Review teams were constituted from the PEPFAR Adult Care and Support TWG based on technical knowledge and ongoing work related to the respective intervention. Where needed, subject matter experts who were not members of the TWG were invited to join the review teams. Each review team included at least three reviewers with subject matter expertise. These review teams constitute the authorship of the 12 intervention-specific articles in this supplement for which a literature review was conducted.

Search strategy

The following databases were searched to perform this literature review: Medline, Global Health, and Embase through Ovid; Cumulative Index to Nursing and Allied Health Literature (CINAHL) through EBSCO; Sociological Abstracts (SOCA) through ProQuest; and African Index Medicus (AIM) through the WHO. Databases were assessed by librarians for their capability to perform complex searches. Aspects of databases considered included strength of controlled vocabulary and indexing, advanced search capabilities, and number of citations indexed by the database. According to capability, simple searches were performed in SOCA and AIM, searches of moderate complexity were performed in CINAHL, and searches of the highest complexity were performed in Medline, Embase and Global Health. Search terms used to perform the review were agreed upon by members of the review teams and two Centers for Disease Control and Prevention (CDC) librarians who performed the searches (GB and EW). Terms were intentionally chosen to produce a broad scope of results relating to HIV/AIDS and the selected interventions.

Base search strategies were created by the librarians to use across all 12 interventions for which the literature was reviewed. These strategies varied according to the capabilities of the databases in which they were performed. Simple base strategies, utilized in AIM and SOCA, used variations of the terms HIV, human immunodeficiency virus, AIDS, Acquired Immunodeficiency Syndrome, and HIV Infections to create filters that addressed HIV/AIDS. More complex base strategies, utilized in CINAHL, built upon the simple base by introducing a filter that addressed the outcomes of interest including morbidity, mortality, retention in care, quality of life, HIV transmission, and cost-effectiveness (Appendix 1). Base strategies of the highest complexity, utilized in Medline, Embase and Global Health, further added a developing countries or resource-limited settings filter in an effort to limit citations to countries and socioeconomic groups of interest to the reviewers (Appendix 2). Additionally, base strategies utilized in Medline and Embase applied a humans-only filter that was not available in other databases. Further intervention-specific terms were applied to these base strategies depending on the intervention and database utilized. These additional terms are listed in the papers relating to the individual interventions in this supplement. All strategies were initially limited to a date range of January 1995 – July 2013. (Several authors updated their literature searches in May 2014; see the intervention-specific articles for details.) Results were inclusive of all publication types and languages.

Search results were exported into individual EndNote libraries by database and combined into large EndNote libraries by intervention. This enabled the librarians to remove duplicate references across databases while maintaining the result counts from individual databases.

EndNote libraries, without duplicates, were exported to Word Documents or sent directly to the reviewers based upon software availability and reviewer preference.

Data analysis

For each HIV care and support intervention, reviewers scanned the citations and abstracts to identify studies that appeared to address the intervention of interest in persons living with HIV (PLHIV) and reported on at least one of the five outcomes of interest (**eligible studies**).

Full-text versions of these studies were obtained and reviewed by the review teams. Studies that, upon full review, did not contain this information were excluded from further analysis. Those that did meet these criteria were included in the review (**included studies**).

Rating the quality of evidence for individual studies

The quality of the evidence from each of the included studies for each outcome of interest was summarised based on the type of study and other factors, such as the number of study participants and internal and external validity of the study data. The overall quality of evidence for each study was rated as S*trong, Medium* or *Weak* on the basis of these factors (Table 2).

Qualitative studies were rated separately using a scale that took into account the research design and methodology, theoretical framework, sampling process, methods of data collection and analysis, and how authors drew their conclusions[6]. Based on this scale, qualitative studies were rated as either: *Level I (Generalizable studies)*; *Level II (Conceptual studies)*; *Level III (Descriptive studies)*; or *Level IV (Single case study)*.

Cost effectiveness

Articles that reported on cost effectiveness were rated separately by a health economist and rated as: *Level 1* - Full economic evaluation [includes Cost-effectiveness analysis (CEA), Cost-utility analysis (CUA), or Cost-benefit analysis (CBA)]; *Level 2* - Partial economic evaluations (i.e. cost analyses, cost-description studies, cost-outcome descriptions); or *Level 3* - Randomized trials and studies (reporting more limited information, such as estimates of resource use or costs associated with the intervention(s) and comparator(s)).

Rating the quality of the body of evidence by outcome

Because of the nature of the review and the review questions as well as the heterogeneity of study populations, study methods, settings, and outcomes, we did not attempt quantitative synthesis of study results overall. Rather, for each intervention, reviewers applied quality measures to each study, grouped the studies by the outcome(s) addressed, and rated the overall quality of the body of evidence for each outcome as *Good, Fair* or *Poor* (Table 3).

Rating the expected impact by outcome

The expected impact of the intervention by outcome was then determined based on the magnitude of effect demonstrated in individual studies, the quality of the body of evidence (all included studies), and consistency across the studies. Expected impact was rated as H*igh, Moderate, Low* or *Uncertain* based on criteria agreed upon by the TWG a priori (Table 4). At least two members of each review team participated in assigning expected impact ratings for individual outcomes.

Data synthesis

Data from included studies were abstracted and entered into an evidence-rating grid. The data elements included: the study identifying information (lead author, title, journal and year published); the type of study [e.g., randomized controlled trial (RCT), controlled trial

without randomization, observational study, systematic review (with or without meta-analysis)]; the quality of evidence for each study; the quality of the body of evidence for each outcome; the magnitude of effect for each study, presented as hazard ratios, odds ratios, or relative risk and 95% confidence intervals; and the overall expected impact for each outcome. These evidence rating grids are included in each of the articles in this supplement.

Weekly conference calls coordinated by the Adult Care and Support TWG co-chairs allowed reviewers from different groups to share progress to optimize adherence to the same general review approach. Each group was asked to summarise their study selection process and present it as a studies flow diagram that included: (i) the total number of citations from the CDC Library (and other sources, if applicable); (ii) the number of abstracts that were deemed eligible for review of the full text articles (**eligible studies**); (iii) the number of full text articles retrieved; (iv) the number of studies excluded upon full text review; and lastly, (v) the number of studies that fulfilled the inclusion criteria (**included studies**). These flow diagrams are included in the intervention-specific articles in this supplement.

Reporting the results of the literature reviews

The results of the 12 literature searches and a summary of the literature about TB screening are included in the 13 intervention-specific articles in this supplement. Each article contains a definition of the intervention of interest; intervention-specific search terms used in the review; a flow diagram indicating the process that led to the studies included in the review; detailed information on the included studies, including an assessment of the quality of evidence and the expected impact of the intervention on each of the outcomes of interest; programmatic considerations important in making decisions regarding implementation of the intervention; and research or informational gaps.

It is the objective of this review and of the participating authors to present information that will be of value not only for PEPFAR in-country USG teams but also for other bi- and multi-lateral donors and host governments in low- and middle-income countries. Further, the authors hope that this information will serve as a resource for discussions on how to prioritize HIV care and support funding to maximize the impact of these interventions on the HIV/AIDS epidemics in these countries.

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Appendix 1

Filter that addressed the outcomes of interest including morbidity, mortality, retention in care, quality of life, HIV transmission, and cost-effectiveness applied in the base search of the care and support intervention evidence review

Variations of the following terms were used to create filters that addressed morbidity, mortality, retention in care, quality of life, HIV transmission, and cost-effectiveness in CINAHL, Medline, Embase, and Global Health.

access

assessment

cost benefit analysis

cost-effectiveness

death rate

disability-adjusted life year

disease

effect

evaluation

health status

HIV long-term survivors

hospitalization

illness

impact

independence

independent

interpersonal relations

intervention

morbidity

mortality

outcome

outpatient

people living with HIV

physical condition

physical fitness

prevention

psychological

psychology

quality of life

resources/services

retention

social behavior

social environment

social relationship

transmission

Appendix 2

Filter for developing countries or resource-limited settings applied in the base search of the care and support intervention evidence review

The following filter was created by Mellanye Lackey at the University of North Carolina (here). It has been adapted for the purposes of this search.

"developing country" or developing countries or "developing nation" or "developing nations" or "developing population"or "developing populations" or "developing world" or "less developed country" or "less developed countries" or "less developed nation" or "less developed nations" or "less developed population" or "less developed populations" or "less developed world" or "lesser developed country" or "lesser developed countries" or "lesser developed nation" or "lesser developed nations" or "lesser developed population" or "lesser developed populations" or "lesser developed world" or "under developed country" or "under developed countries" or "under developed nation" or "under developed nations" or "under developed population" or "under developed populations" or "under developed world" or "underdeveloped country" or "underdeveloped countries" or "underdeveloped nation" or "underdeveloped nations" or "underdeveloped population" or "underdeveloped populations" or "underdeveloped world" or "middle income country" or "middle income countries" or "middle income nation" or "middle income nations" or "middle income population" or "middle income populations" or "low income country" or "low income countries" or "low income nation" or "low income nations" or "low income population" or "low income populations" or "lower income country" or "lower income countries" or "lower income nation" or "lower income nations" or "lower income population" or "lower income populations" or "underserved country" or "underserved countries" or "underserved nation" or "underserved nations" or "underserved population" or "underserved populations" or "underserved world" or "under served country" or "under served countries" or "under served nation" or "under served nations" or "under served population" or "under served populations" or "under served world" or "deprived country" or "deprived countries" or "deprived nation" or "deprived nations" or "deprived population" or "deprived populations" or "deprived world" or "poor country" or "poor countries" or "poor nation" or "poor nations" or "poor population" or "poor populations" or "poor world" or "poorer country" or "poorer countries" or "poorer nation" or "poorer nations" or "poorer population" or "poorer populations" or "poorer world" or "developing economy" or "developing economies" or "less developed economy" or "less developed economies" or "lesser developed economy" or "lesser developed economies" or "under developed economy" or "under developed economies" or "underdeveloped economy" or "underdeveloped economies" or "middle income economy" or "middle income economies" or "low income economy" or "low income economies" or "lower income economy" or "lower income economies" or "low gdp" or "low gnp" or "lower gdp" or "lower gnp" or lmic or lmics or "third world" or "lami country" or "lami countries" or "transitional country" or "transitional countries" or Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America or Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or

Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brazil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or "Lao PDR" or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or "Saint Kitts" or "St Kitts" or Nevis or Saint Lucia or St Lucia or "Saint Vincent" or "St Vincent" or Grenadines or Samoa or Samoan Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia or Western Sahara or Kuwait or United Arab Emirates or Qatar or Nauru or Tuvalu or Bahamas or South Africa or South Sudan

Table 1

Care and support interventions included in this supplement

	Intervention
1.	Cotrimoxazole (CTX) prophylaxis
2.	Tuberculosis screening
3.	Isoniazid preventive therapy (IPT)
4.	Positive Health, Dignity, and Prevention (PHDP)/Prevention with Positives (PwP)
5.	Viral hepatitis—hepatitis B virus (HBV) surface antigen screening
6.	Malaria prevention (cotrimoxazole and insecticide treated nets)
7.	Safe Water, Sanitation and Hygiene (WASH)
8.	Prevention of cryptococcal meningitis (cryptococcal antigen screening and treatment)
9.	Nutritional Assessment, Counseling and Support (NACS)
10.	Screening and treatment to prevent cervical cancer
11.	Mental health and substance/alcohol abuse
12.	Social services
13.	Support groups

Table 2

Criteria for rating the quality of evidence* for individual studies

Level of evidence	Description
1=STRONG	Systematic review/meta-analysis of randomized controlled trials (RCTs) with consistent findings; high-quality individual RCT
2=MEDIUM	Systematic review/meta-analysis of lower-quality clinical trials or of studies with inconsistent findings; lower-quality clinical trial; cohort study; case-control study
3=WEAK	Consensus guidelines; usual practice; expert opinion; case series

*Criteria for rating the quality of evidence for each study were adapted from the U.S. Preventive Services Task Force Procedure Manual[7]. For purposes of these reviews, ratings could be modified by other factors, including the number of study participants and an assessment of the internal and external validity of the study data.

Table 3

Criteria for rating the quality of the body of evidence* by outcome of interest

Rating	Description
1= GOOD	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes
2= FAIR:	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.
3= POOR	Evidence is based on consensus, usual practice, opinion, or case series. Additionally evidence is insufficient to fully assess the effects on health outcomes because of limited number, or power of studies, important flaws in design or conduct, gaps in the chain of evidence, or lack of information on importance on the key health outcomes

*Adapted from the US Preventive Services Task Force Procedure Manual[7].

Table 4

Criteria for rating the expected impact of the intervention on the outcome of interest

Rating	Description
1= HIGH	Intervention expected to have a **high** impact on the outcome
2= MODERATE	Intervention likely to have a **moderate** impact on the outcome
3= LOW	Intervention expected to have a **low** impact on the outcome
4=UNCERTAIN	Available information is not adequate to assess impact on the outcome