Strategies for Improving the Lives of Women Aged 40 and Above Living with HIV/AIDS

I. Background and Objectives for the Systematic Review

It is predicted that by 2020, half of persons living with HIV infection in the United States will be 50 years of age or older.¹ This is a result of better HIV treatment, leading to increased survival, as well as an increasing population of older men and women contracting HIV. Many will also be living with the comorbidities and chronic medical conditions that occur with aging. For women living with HIV beyond menopause, in particular, there is a major gap in the understanding of how HIV will affect their lives, and approaches to optimal care are not clear. Further complicating the issue is the fact that the natural history and prognosis of HIV/AIDS among men and women living longer with HIV and those newly infected at an older age appear to be distinct.²

Comorbidities (infectious and non-infectious) related to HIV or aging are of course not a unique concern for older women, but the approach to care and the understanding of the disease process may be influenced by sex/gender and race/ethnicity. The comorbid conditions of interest include cardiovascular disease, hypertension, type-2 diabetes, obesity, chronic kidney disease, bone disease, hyperlipidemia, cancer, depression, and neurocognitive impairment. HIV-positive antiretroviral-treated aging women who achieve viral suppression are in a generalized status of immune activation and therefore may be at an increased risk of age-associated end-organ diseases compared to uninfected age-matched controls.³

There have been inconsistent and inconclusive reports regarding HIV and menopause. Some studies report menopause at an earlier age among HIV-infected women.⁴⁻⁹ However, many of these studies have a small sample size, involve only HIV-infected cohorts without a control, or do not account for confounding factors, such as history of drug use, current smoking, lower BMI, or race. Menopausal transition may affect a woman’s quality of life by altering her mood or causing sexual dysfunction. It also accelerates the onset and progression of chronic diseases of aging, including cardiovascular disease, hypertension, diabetes, and reduced bone mineral density.¹⁰⁻¹⁵ For example, the prevalence of osteoporosis ranges from 7.3% to 84% in HIV-infected postmenopausal women and 0.7% to 23% in HIV-uninfected postmenopausal women.¹⁴ This suggests a possible increased burden of disease for HIV-infected women if they enter menopause at an earlier age and are living longer lives because of effective ART treatment.¹⁵ The effect of hormonal replacement therapy, as well as drug/drug interactions with antiretroviral treatments, is also not well elucidated.

Polypharmacy is common among older patients. The problem of drug/drug interactions and possible increased side effects between antiretrovirals and the numerous other medications taken for chronic diseases can pose significant clinical problems. The pharmacokinetics/pharmacodynamics of several medications may also be altered with increasing age and changes in weight and metabolism.¹⁶,¹⁷

Although older women have been found to have lower rates of substance abuse compared to younger women, they may be more vulnerable to the effects of drugs, including alcohol.
Moreover, in lesbian and bisexual women, older age does not appear to be associated with a decrease in alcohol and drug use.\textsuperscript{18-20}

Older adults with HIV infection are more likely to be depressed and lonely.\textsuperscript{21,22} Although HIV has been associated with neurocognitive symptoms, including dementia, and some studies suggest more impairment in HIV-infected women compared to HIV-uninfected women,\textsuperscript{23} few studies have evaluated older women exclusively. Many older HIV-infected women face issues of stigma, poverty, sexual violence, and changes in relationships, including divorce/separation/death of a partner. Many are burdened with taking care of elderly parents or grandchildren.\textsuperscript{24}

Furthermore, special consideration should be given to women who identify as lesbian, bisexual or transgender. For women who identify as lesbian, while HIV transmission is generally low after unprotected lesbian sex, a woman may have contracted the virus from a past heterosexual experience, or through other routes. This may lead to delayed diagnosis and greater disease burden for the individual. Transgender women (people who were born male but identify as female) are also vulnerable, for medical and social reasons, as they may get hormonal therapy to change their appearance, which can impact their risk for many diseases,\textsuperscript{25,26} and are often subjected to violence, and face depression, and stigma.\textsuperscript{27} Transgender men (people who were born female but identify as male) who live with HIV, likely face similar issues.

The care of older HIV-infected women should integrate biomedical, behavioral, and social science interventions.\textsuperscript{17} Our current system of care does not support a comprehensive model that can provide a tailored approach for older HIV-infected women. Women have to move between a primary care provider, a gynecologist, and several specialists (HIV/infectious disease, cardiologist, neurologist, nephrologist, and endocrinologist, to name a few) for their medical needs. There are few centers that provide comprehensive psychosocial and case-management services for older HIV-infected women. Many health care providers have not been trained to deal with an aging population with HIV. Even current guidelines for HIV testing, HIV treatment, and comorbidities and HIV-related opportunistic infections are disease specific and do not explicitly address aging patients (there are adolescent and pregnancy related guidelines). All of these issues hinder the provision of individualized care. If we are to succeed in improving the current cascade of care for HIV-infected women (diagnosis, access to care, adherence and retention in care, sustain a below detectable plasma viral load, and decrease morbidity and mortality), we need to provide a practical and accessible system of care for this aging population.

We plan to develop an evidence map characterizing empirical studies that pertain to older women who live with HIV and apply to today’s US setting, and to outline resources that are available to these women, in a purposeful sample of 6 states. We will engage Key Informants (KIs) to refine the design of the evidence map and interpret its findings, and to supplement identified information on available resources. We use the term “resources” to refer to implemented programs that provide [healthcare and other] services, or to specific services. Insurance and non-insurance policies can promote or facilitate access to resources.

II. Overview of the Technical Brief

The Technical Brief comprises an evidence map and an outline of resources that are currently available in six states. Details on the approach are provided in the Methods section.
The evidence map will be a compendium of empirical studies that pertain to older women who live with HIV. Eligible studies will be organized in three interest areas, comprising studies that

1. **Measure the impact of existing resources (individual services or programs bundling services) on outcomes.** These include studies describing:
   a. Comparisons of using a resource versus not using it, or versus using another [version of the] resource.
   b. Modifiers of the likelihood that a woman will engage or continue being engaged with a resource.

2. **Measure the impact of insurance** on outcomes, including assessments of person- or system-level modifiers of access to insurance or the impact of insurance.

3. **Assess the performance of diagnostics for co-occurring disease; and assess the effects of treating co-occurring diseases (such as depression) or risk factors (such as high blood pressure) on person-level outcomes.** Assess co-occurring diseases and risk factors as predictor of all-cause mortality and HIV progression.

The Methods Section includes details on the eligibility criteria for the evidence map.

In addition, we will outline which resources appear to be available to older women who live with HIV in a purposeful sample of six states, namely Rhode Island, New York, Texas, California, Mississippi, and Alabama. We motivate these choices in the Methods section.

### III. Analytic Framework

The Figure shows an analytic framework for the evidence map, for the three interest areas. For the first interest area (measuring the impact of resources), older women who live with HIV may engage with resources, transiently, or in a continued fashion, and this engagement affects person- and system-level outcomes. A range of modifiers affect the likelihood of engaging or continue engaging a resource, including insurance status, sociodemographic (e.g., race/ethnicity, educational attainment), psychosocial (social support), and cultural factors. The second interest area includes studies that measure the marginal effect (overall impact) of insurance on person- and system-level outcomes, irrespective of whether the impact of insurance is mediated by women’s use of specific resources or through other mechanisms. Again, a range of modifiers affect the likelihood that insurance impacts on outcomes. The third interest area includes studies that assess the performance of tests for diagnosing co-occurring diseases, and of treatments for managing such diseases on person-level outcomes, and predictive models of all-cause mortality or HIV progression.
IV. Methods

The evidence map will be a compendium of empirical studies that apply to older women who live with HIV in today’s US setting.

Eligibility Criteria

Eligible populations

Eligible populations are older women who live with HIV, irrespective of when they first contracted the infection. We will use 40 years of age as an age cutoff, to include premenopausal women who are less likely to bear children, as well as peri- and postmenopausal women. Studies with broader enrollment, e.g., enrolling both sexes or all ages will be excluded, unless they report results for strata where at least 80% of the participants are older women who live with HIV.

Eligible outcomes

All patient-level outcomes and system-level outcomes are eligible. Examples of person-level outcomes include clinical outcomes such as mortality and morbidity, mental health, function, quality of life (however measured), likelihood of adherence to eligible interventions, and out-of-pocket costs. Examples of system-level outcomes include total costs, and changes in the proportion or number of women engaged with a resource.
Eligible interventions and exposures and study designs, by interest area

For the first interest area, eligible resources include specific services that give medical, behavioral or social support, or programs that bundle several such services. This definition is quite broad and encompasses any organized structure (process) that supports women’s wellbeing. The following are indicative examples: A clinic providing routine HIV care or mental health care is an example of a service providing medical support. A program for helping women facing addiction problems may provide medical, behavioral and social support. A structure that assists women to apply for Ryan White programs is an example of a service providing social support. Eligible studies must

1. Inform on the impact of a resource on person-or system-level outcomes. Eligible is any longitudinal design that allows, even under strong assumptions, estimation of the impact of a resource, including randomized trials, non-randomized comparisons of cohorts, and before-after studies. Studies that simply describe the implementation of a new service without any assessment of its impact on person- or system-level outcomes are not eligible.

2. Alternatively, assess modifiers of initial or continued engagement with a resource (as defined by the authors). Eligible are cohort, case-control or cross-sectional studies assessing the association between initial or continued engagement with a resource and person-level factors, including sociodemographic or cultural factors (e.g., race/ethnicity, income, immigrant status, marital status, insurance coverage, highest educational attainment), psychosocial factors (e.g., social or family support), criminal history, or clinical, personal and family medical and mental history factors (e.g., cancer, heart disease, addition problems, mental health problems); or resource-level factors (e.g., cost for participation, case management, multidisciplinary team). Eligible also are surveys or qualitative research analyses of people’s opinions on the barriers they face.

For the second interest area eligible are studies that assess the association between different levels of insurance coverage and person- or system-level outcomes. Any comparative design is eligible including randomized trials, nonrandomized comparisons of cohorts, and before-after studies. The effects of insurance must be assessed longitudinally.

Finally, the third interest area includes studies about the diagnosis of co-occurring diseases and management of risk factors and of co-occurring diseases, and about prediction of all-cause mortality or HIV progression.

1. Eligible are studies of the performance of tests, including imaging tests, laboratory measurements, and clinical scores, for diagnosing the presence of co-occurring diseases, including but not limited to infections such as hepatitis C, tuberculosis, and opportunistic infections, cancers, or dementia. Eligible designs include cross-sectional, case-control and cohort studies.

2. For assessing the effectiveness and safety of treatments for co-occurring diseases or risk factors, eligible are randomized and nonrandomized comparative studies. Examples of co-occurring diseases of interest include cancer, infections (including hepatitis C, human papilloma virus [HPV], tuberculosis, osteomyelitis, AIDS defining infections such as Pneumocystis carinii pneumonia [PCP], etc.), neurocognitive impairment (including
HIV-associated dementia), cardiovascular disease, mental health (depression, PTSD, bipolar, schizophrenia), addiction and substance abuse (heroin, cocaine, prescription drugs, alcohol, smoking, “party” drugs such as MDMA [Ecstasy], Flunitrazepam [Rohypnol], Ketamine), musculoskeletal disease (e.g. osteoporosis, rheumatoid arthritis) and other age-associated end-organ diseases not mentioned here (by reviewer consensus). Risk factors of interest include established risk factors for major diseases such as hypertension and blood pressure measurements, hyperlipidemia, diabetes, obesity, osteoporosis and low bone mineral density measurements.

3. For predictive models of all cause mortality or HIV progression, eligible are longitudinal epidemiologic studies that model risk of (or time to) all cause mortality, AIDS defining illnesses, or changes in viral load or CD4 cell count. For feasibility, we demand that the abstract clearly states that such a model was developed or validated.

Additional eligibility criteria

Because the scope that corresponds to the three interest areas mentioned in the Overview is very large, we make the following operational decisions.

First, we will not consider research completed longer than 10 years ago (specifically, earlier than 01/01/2005), because older empirical data are less likely to be relevant to today’s setting. While it is plausible that earlier studies are applicable, important questions are often addressed by more recent replication studies, in which case they would be represented in the evidence map. Further, the more recent literature is probably more relevant for informing the future research agenda.

Second, because the main focus of the Technical Brief is to inform about the US setting, we will generally not consider studies conducted exclusively in other countries. This is probably most defensible for empirical studies pertinent to the first two interest areas (impact of resources on outcomes, and impact of insurance), which deal with questions that are quite specific to the US health system. Arguably, empirical studies in the third area of interest (diagnosis and management of comorbid conditions and predictors of patient-centered outcomes) are applicable irrespective of whether a study is conducted in the US or in another country with advanced healthcare. We plan including only studies conducted in US settings, but we will examine the feasibility of not limiting to US settings for empirical studies in the third interest area.

We will exclude studies not reporting empirical data, such as theory expositions, modeling studies of the effects of policies, opinion pieces, and non-systematic reviews. However, we will record and characterize systematic reviews of eligible studies. We will consider as systematic reviews that report using a search strategy and explicit eligibility criteria.

We will include studies that have a sample size of at least 100. Smaller sample sizes are unlikely to result in precise estimates, and thus the utility of recording them in the evidence map is questionable. A higher cutoff may indeed have to be selected, as informed by a random sampling of the evidence-base.
Literature Search Strategies for Identification of Relevant Studies

We will search PubMed, PsycINFO, and SocINDEX. We will coordinate with the social sciences librarian at Brown for suggestions of additional databases. We will search for terms related to HIV or AIDS, crossed with and general terms on interventions, policies, services, or programs. We will limit results to studies published after 01/01/2005, published in English, and having at least one author with a US affiliation, as described in the eligibility criteria. We will exclude publications that are not indexed as empirical studies (e.g., addresses, autobiographies, lectures). Because publications can take up to 6 months to be fully indexed, we will search using only free text terms for studies published in the last year.

Outlining Available Resources in A Purposeful Sample of Six States

We will outline which resources appear to be available to older women who live with HIV in a purposeful sample of six states, namely Rhode Island, New York, Texas, California, Mississippi and Alabama. We will perform systematic web searches, emulating a web-savvy, persistent patient or provider who is not familiar with the resources available in these states, and who wishes to find information about them. This will inform on the ease with which one can identify local resources. To capture variability between urban and rural settings we will attempt to distinguish resources available in the largest city of each state, and to rural areas.

We will obtain input from the Task Order Officer (TOO), the sponsoring partner and the KIs before finalizing the list of states to examine. Our tentative list includes New York, [southern] California, Texas, Mississippi and Alabama. These states are diverse in terms of geographical location, HIV prevalence overall and among women, political culture, health systems, per capita income, proportion of women with HIV who are foreign born or belong to a racial minority. For example, New York, Texas, and [southern] California are among the regions with the highest number of women and girls living with HIV infection in the nation. Alabama and Mississippi are important because of their proportionally large number of African American women who live with HIV. We intend on focusing on resources available in [southern] California, rather than the San Francisco/bay area, which may be a special case because of the large number of programs and services focusing on men who live with HIV.

Data Abstraction and Data Management

The evidence map will include extraction of a structured set of elements on the population, the exposure or intervention, and examined outcomes (P[E/I]CO).

The attributes of the P(E/I)CO elements to be extracted will be discussed with the KIs and the TOO. Each study will be classified into the three areas of interest. The following descriptions of items to be extracted are not exhaustive and are subject to revision:

1. For populations, we will record information on sample size (largest analysis pertinent to older women living with HIV); period of enrollment; mean age and age range; race/ethnicity groups representing at least 20% of the study sample (e.g., African American/Black, American Indian/Alaska Native, Asian, Hispanic/Latino, Native Hawaiian/Other Pacific Islander, or White); whether the study focused on women who belong to one of the following strata (as yes/no/unclear): illegal immigrants, HIV contracted early vs late (before vs after 40...
y), partner or other support available vs not, burdened with dependent care vs not, transgender women vs not, lesbian or bisexual women vs not, sexual monogamy vs not, pre- or peri-menopausal vs post menopausal, low income vs not, low educational attainment (no completion of highschool) vs not, insured vs not, engaged with the prison system vs not, experiencing violence vs not, experiencing mental health issues vs not, battling substance abuse vs not.

2. For services and programs and other interventions, we will record whether they provide medical, behavioral, or social support, or a combination thereof. These interventions are complex, in that they have many versions and are likely to interact with characteristics of the setting or the population. In addition, it may be meaningful to categorize services and programs based on whether they are community- or health center-based; are administered by health, behavioral health or human service professionals vs not; include case managers/patient navigators or not).

3. In terms of outcomes, we propose to record whether there is information on general clinical outcomes (including overall or cause-specific mortality [including suicides], and outcomes related to major comorbidities including infarctions, strokes, and fractures), HIV- and AIDS-related outcomes (e.g., virologic outcomes and development of AIDS), quality of life (using validated instruments), and mental health outcomes.

To maximize the utility of such an evidence map for the Office for Women’s Health and the research community, we plan on making available implementations of modern literature identification methods (using machine learning) that can help the continuous monitoring of the evidence base after the conclusion of the Technical Brief and facilitate keeping the evidence map current. We will use semi-automated machine learning algorithms developed and implemented in the Abstrackr software by our team. Based on screeners’ labeling of abstracts (accept/reject), Abstrackr can predict the likelihood of whether future abstracts are relevant. We will make these trained algorithms publicly available for the benefit of the Office for Women’s Health and the research community to facilitate updating the evidence map in the future.

Assessment of Methodological Risk of Bias of Individual Studies

Not applicable for the purpose of this Technical Brief.

Data Synthesis

We will summarize KI input and use it to inform the design of the evidence map, in terms of the data items to be extracted; to identify important evidence gaps; and to prioritize gaps into research needs. All analyses will be qualitative and descriptive.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

Not applicable for the purpose of this Technical Brief.

Assessing Applicability

Not applicable for the purpose of this Technical Brief.
V. References


15. Imai K, Sutton MY, Mdodo R, Del Rio C. HIV and Menopause: A Systematic Review of the Effects of HIV Infection on Age at Menopause and the Effects of


Source: www.effectivehealthcare.ahrq.gov
Published online: March 1, 2016
VI. Definition of Terms

We use the phrase *older women who live with HIV* to denote HIV-infected women who are of middle age (about 40 years) or older. The age cutoff is approximate, and meant to include premenopausal women who are less likely to bear children, as well as peri- and postmenopausal women.

We use the term *resources* to refer to implemented programs that provide [healthcare and other] services, or to specific services. Unless otherwise noted, we refer to resources available to or intended for older women who live with HIV.

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol, to facilitate tracking. Example table below:

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<thead>
<tr>
<th>Date</th>
<th>Section</th>
<th>Original Protocol</th>
<th>Revised Protocol</th>
<th>Rationale</th>
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<tr>
<td>The effective date of the change</td>
<td>Where the change would be found in the protocol</td>
<td>Original protocol language</td>
<td>Changed protocol language</td>
<td>Justification for the change, and, as applicable, potential for bias.</td>
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VIII. Key Informants (KIs)

KIs are end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the KIs’ role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from KIs when developing questions for systematic review or when identifying high priority research gaps and needed new research. KIs are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

KIs must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as KIs and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

IX. Peer Reviewers
Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

X. EPC Team Disclosures
EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XI. Role of the Funder
This project was funded under Contract No. HHSA290201500002I (Task Order #6) from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The TOO will review contract deliverables for adherence to contract requirements and quality. The authors of this report will be responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.