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A systematic review of prevalence and predictors of frailty in individuals with HIV

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Systematic Review of Frailty in HIV

Abstract:

Background: Aging of the HIV positive (HIV+) cohort has introduced the challenges of managing comorbidities and syndromes traditionally associated with older adults. Frailty, a state of vulnerability to stressor events that is associated with adverse functional outcomes has been demonstrated in HIV+ individuals, with varying prevalence across the studies.

Objectives: To describe the prevalence and predictors of frailty in individuals living with HIV using systematic review methodology.

Methods: We searched Medline, CINAHL, EMBASE, PsychInfo and PubMed for original observational studies with populations inclusive of HIV+ individuals in which frailty was assessed using the frailty phenotype or a variant thereof. Studies were examined for frailty prevalence and key predictors of the syndrome in those with HIV.

Results: 13 of 322 citations were included for full review. All demonstrated the presence of frailty in HIV with prevalence ranging from 5% to 28.6% depending on population studied. HIV was a risk factor for frailty when compared to those without HIV. Key predictors of frailty included increasing age, presence of comorbidity, an AIDS diagnosis and low current CD4+ cell count.

Conclusions: HIV appears to be an independent risk factor for frailty, with frailty occurring in HIV+ individuals at rates comparable to older HIV negative cohorts. Accurate description of the problem is hampered by heterogeneity in study populations and frailty assessment measures. Future longitudinal work with standardised methodology is needed to accurately describe prevalence and confirm the key predictors.

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Frailty
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Aging

Introduction:

Improved survival with modern combined anti-retroviral therapy (cART) alongside increased later life acquisition of HIV is driving an increase in the age of the HIV-positive (HIV+) cohort. HIV in the older individual presents a number of challenges, including an excess in comorbidities not traditionally associated with HIV infection (1) including falls (2), functional impairment (3) and frailty (4), which feature more commonly in older HIV-negative (HIV-) 'geriatric' populations. Whether HIV itself or treatment toxicities cause premature or accelerated aging is subject to ongoing debate (5,6) and is considered research priority(7).

With an ever increasing number of older adults engaged in HIV care, services will need to adapt to meet their complex needs. In general chronological age may not be the best predictor of prognosis or individual need (8) and a more useful model for risk stratification may be the presence or absence of frailty. Frailty describes a state of increased vulnerability to stressor events resulting from declines in multiple physiological systems. When present, frailty is associated with adverse outcomes including falls, hospital admission and death(9–11). The difficulty in using frailty as a concept is the lack of consensus definition, particularly regarding how it should be measured(12). The most widely used model in both HIV+ and HIV- populations is the frailty phenotype (FP) (13) characterised by Fried et al(9). The FP comprises five criteria; weight loss, exhaustion, low physical activity, weak grip strength and slow walking speed; with frailty defined by the presence of three or more criterion. Those with one or two are classed as pre-frail and none as robust(9).

There is heterogeneity in HIV frailty research with different authors using various measures and definitions of frailty making it difficult to fully quantify the burden of frailty in the context of HIV. We therefore aim to conduct a systematic review of the original literature pertaining to frailty prevalence and predictors in individuals with HIV, using the FP as a standard model.

Methods

Search Strategy

We aimed to identify observational studies assessing frailty status in individuals with HIV. We therefore conducted a systematic electronic search using the following Healthcare databases; Medline, CINAHL, EMBASE, PsychInfo and PubMed. They were searched from January 2000 to April 2014, using database appropriate MeSH terms alongside "HIV", "Human Immunodeficiency Virus", "Acquired Immunodeficiency Syndrome" combined with "frail*", "reduced functional reserve", "functional impairment", "reduced physiological reserve", and "physiological vulnerability". Broad 'function' terms were used to capture studies where frailty was part of wider functional assessment. International HIV/AIDS conference abstracts and major HIV and Gerontology journals were also searched. Additionally, reference lists of relevant review articles and articles reviewed at full-text stage were screened by hand to identify potentially missing studies.

Eligibility Criteria

In article selection we applied the following inclusion criteria: (i) original observational research presented; (ii) frailty defined using the Fried FP, or modified variant thereof, to

allow standardisation. We therefore excluded studies published before its description in 2001. (iii) Inclusion of data on HIV+ adults; (iv) frailty prevalence for HIV+ individuals should be stated, easily calculable or obtainable from authors. Studies not meeting the above criteria were excluded. Though language was not an exclusion criterion or limit set during database searches, all citations found were written in English.

Study selection

Selection for full text review was independently conducted by two reviewers (TL and FC), by applying eligibility criteria to the title and abstract. Articles deemed relevant, or where further clarification of eligibility was required, were retrieved for full text review. Authors were contacted where points of clarification were needed(14–17). The reviewers independently assessed selected full text articles and after discussion and consensus review where needed (by MF) a list of studies for inclusion was finalised.

Quality Assessment

We evaluated study quality, with respect to bias using the Newcastle-Ottawa Scale (NOS)(18). The NOS is a method of quality assessment for non-randomised studies with scales available for different observational methodologies, which were applied in this case depending on study type. Broadly the NOS criteria evaluate quality in three domains: Selection; Comparability and Outcome, awarding a designated number of stars to each study in each domain depending on whether quality markers are met. We adapted the scale for cross-sectional studies by reducing the weight allocated to validation of exposure (HIV) and outcome (frailty), to be awarded one rather than two points, making weighting comparable to that awarded for cohort/case-control scales, preventing artificially high quality scoring of cross-sectional studies. Given the importance of statistical analysis, scoring for an appropriate approach was substituted into schemes for cohort and case-control study design types.

Data Extraction

A data extraction form was designed and independently applied to each study by TL and FC. Data was extracted on study design, population characteristics, frailty definition and frailty prevalence (for HIV+ and HIV- where control groups included) along with significant frailty predictors. Data extracted by each reviewer were compared for consistency and any disagreements resolved by consensus or use of a third reviewer (MF).

Statistical Analysis

We planned to conduct a meta-analysis of frailty prevalence to generate a summary prevalence with corresponding 95% confidence interval. Comprehensive Meta-analysis software (Englewood, USA) was used. A random effect meta-analysis on the included studies presenting cross-sectional data was performed(14,19–24), producing summary prevalence of 8.6% (95% CI 6.5 to 11.3). However heterogeneity was high with an I-squared score of 77.63, which did not reduce to below 75 with sensitivity analysis when additional factors were considered including country of origin (US versus non-US), ethnicity (Caucasian versus black predominance), age (average age above/below 50) or ART use (all versus some). Given that variability in prevalence is largely due to heterogeneity across the studies we have chosen not to present the findings as a meta-analysis further. In order to assess potential publication bias we created a funnel plot (figure 1), which owing to the limited

number of studies in our review cannot provide conclusive evidence. However, from the observed funnel plot the spread of studies is more or less symmetrical, suggesting an absence of publication bias,

Results

Search results and study selection

Literature review found 322 citations, 275 from database searches and 47 from index searching of bibliographies, journals and conference proceedings. Of these 103 were duplications and a further 178 excluded after title/abstract review due to non-relevance. 41 were selected for full text review, with a further 28 exclusions due to duplicated presentation of data (6), lack of frailty assessment (12), frailty not defined by FP (4) or absence of primary data (6). 13 studies met full inclusion-criteria. Selection and exclusions shown in figure 2.

Study characteristics

Of the 13 studies selected five were of cohort design (two prospective, three retrospective) (15,17,25–27), with four presenting data from the Multicentre AIDS cohort study (MACS) (17,25–27). One study used case-control design(22) and seven were cross-sectional (19–21,23,24,28) (one nested within a prospective cohort) (14). 11 were presented in full article format and two as conference abstracts. Studies were largely urban community or University clinic based, with only one from a resource-poor setting(22). Studies varied in size from 41 to 2150. Studies were mainly US based (11/13) with the two remaining studies from Mexico and South Africa. All utilised a frailty assessment based on FP criteria, with the three retrospective cohort studies utilising a frailty related phenotype (FRP) comprised of four rather than five criteria as grip strength data was lacking (25–27). One study measured phenotypic criteria differently to other studies (28). General study characteristics and description of frailty parameters are shown in table 1.

Quality

Quality as assessed using design-specific NOS showed that out of a maximum available nine points there was a range from three to eight, with lower quality scores assigned to conference abstracts as shown in table 2.

Frailty prevalence

Prevalence was measured in two ways across the studies. Where cross-sectional data was presented the prevalence was provided for individuals and ranged from 5% in the Mexican study (23) to 28.6% in the MACS cohort (17). In the included MACS articles frailty was assessed on multiple occasions allowing for prevalence to be calculated using total number of individuals as the denominator (based on at least one visit with frailty), ranging 13.9 to 28.6% and using total person visits as the denominator, which resulted in lower prevalence (5.4 -12%) (17,26). Across the MACS timeline, prevalence of frailty in terms of person-visits decreased from 7.6% in 1994-95 (pre-cART era) to 4.5% in 2000-2005 (post-cART era) with increases in median age from 41 to 48 and proportion of those on treatment from 42.3% to 80.2%. In the most recent evaluation, from 2007-2011 (established cART era) where frailty was assessed prospectively with the addition of grip strength, prevalence had risen to 12% of person visits or 28.6% of individuals with at least one frailty visit, along with further

increases in median age to 53.8 and in proportion receiving cART from 80.2% to 84.2%. Piggott (15) presents data from the ALIVE cohort including HIV+/- individuals with past or present intravenous drug use (IDU), in which FP was present in 12.3% of all participants and 12.4% of person visits. Dividing participants by HIV status, 14.6% of HIV+ and 11.3% HIV- were frail (data provided by author).

Predictors of frailty

HIV status

Five studies included HIV- controls. The MACS cohort examined frailty pre-cART introduction (25) where the prevalence of FRP in HIV- participants was 1.5%. In this study, for years 1994-1996, the OR adjusted for age, ethnicity and education for expressing FRP in HIV+ individuals compared to HIV- was 10.97 (95% CI 6.37-18.88) when all person-visits were analysed. This reduced, but remained significant at 4.49 (95% CI 1.98-10.09) when weight loss, which had high association with HIV pre-cART, was removed as a FRP criterion. With established cART Althoff (for MACS) demonstrates a significantly higher frailty prevalence in HIV+ compared to HIV- men (12% vs. 9% p=0.002) (17). Further support for an association with HIV status is provided in the ALIVE cohort where HIV was associated with a 66% increased likelihood of frailty (aOR 1.66; 95% CI 1.24-2.21) (15) and in Pathai's study where the adjusted OR of frailty in those with HIV was 2.14 (95% CI; 1.16-3.92) (22).

Age

In the pre-cART MACS, a 10-year increase in age was associated with a significantly increased risk of frailty with OR 1.61 (95% CI 1.21-2.15), which reduced but remained significant when AIDS was excluded (OR 1.53, 1.11-2.11) (25). This persisted in the cART era (1996-2005) with a 10-year age increase associated with an OR 1.52 (95% CI 1.24-1.87) (26). In later MACS data from 2007-2011, the proportion of visits where frailty was demonstrated increased with increasing age (17). Age was significantly associated with frailty in two additional studies (15,21). In Pathai's South African study, increasing age was a significant predictor in HIV+ women but not men (OR 2.50, CI 1.35–4.58), in a predominantly female HIV+ cohort (73.1%) (22). Ianas showed no association with age and frailty after controlling for CD4 count, but increasing age was significantly associated with lower CD4 count, which did predict frailty (20).

Socio-demographic factors

Studies varied in socio-demographic factors presented. In early MACS analysis pre-1996 (25), college education was associated with frailty, however post-1996 the converse is seen with lower educational attainment associated with (OR 1.73 95% CI 1.19-2.50) (26) and conversion to frailty (17). This association between frailty and lower educational achievement is supported by Onen but not others (21). Ethnicity (non-Hispanic black) was only associated with frailty in the MACS cohort post-1996 (26,17). Unemployment and low annual income were significantly associated with frailty in two studies (19,21) but not reported elsewhere.

Co-morbid conditions

Compared to robust individuals with HIV, those with frailty had significantly more comorbidities (15,17,19,21). The most consistently replicated of which include psychiatric disease, particularly moderate to severe depression (19,21,26,17), cognitive impairment

(21), chronic kidney disease (21,17), diabetes (17) and low BMI (21,22). Hepatitis C co-infection was only associated with frailty in one study and was restricted to those aged 50 and over (20).

HIV factors

CD4+ cell count

Reduced CD4+ count was the most consistently reported HIV factor associated with frailty, with current CD4+ (14,15,19,22,25,26,17) more predictive than nadir count, which only showed significant association in one study (21). In MACS, median CD4+ count increased over the duration of the study with corresponding drop in frailty prevalence overall. However, the risk of frailty increased as CD4+ fell, with adjusted OR for FRP (with 95% CI) of 2.80 (1.97-3.98), 1.98 (1.57-2.50) and 1.36 (1.22-1.50) for CD4+ counts of 100, 200 and 350 cells/mm^3 respectively (26). This CD4+ relationship was also observed within one cross-sectional study, with frailty prevalence 43.5%, 19.2% and 7.8% for CD4+ of <200, 200-350, >350 cells/mm^3 respectively (20). A high CD4+ count was protective of frailty in one study, with CD4+ >750 cells/mm^3 associated with OR 0.66 (95% CI 0.57-076)(26). Importantly, CD4+ count remained a strong predictor of frailty even in those with viral suppression, and when AIDS and comorbidities such as TB and hepatitis C were controlled for (22,26).

Viral load

Viral load (VL) is not as strongly associated with frailty as CD4+ count, with positive association observed only in pre-cART MACS where those with VL >50,000 copies/ml had 2.91 the odds of FRP (95% CI 1.08-7.85) than those without (25). Frailty remained more common in those with VL>50,000 in the post-cART era but not significantly so after adjusting for CD4 count (26). Other studies report no significant association with peak or current VL or virological failure on treatment (15,19,20,22).

AIDS

Where the relationship between AIDS (not including CD4+ <200 cells/mm^3) and frailty was examined, all but one study (19) showed the risk of frailty to be higher in those with AIDS. In MACS, risk was reduced following the introduction of cART, with OR for FRP with AIDS 9.89 (95% CI, 4.70–20.80) and 3.34 (95% CI, 2.24-4.94) pre- and post-cART respectively (26). Such association was less evident in a study of women, where the elevated risk of frailty was only seen in univariate (OR 1.55; 1.03-2.34) and not multivariate analysis and when AIDS was excluded frailty prevalence in those with HIV was 7% compared to 8% in negative controls (14). Lastly those with AIDS had an increased likelihood of becoming frail over those without (OR 1.57; 1.06-2.34) (17).

Discussion

Our systematic review found multiple studies which all demonstrated the occurrence of frailty in adults living with HIV. Frailty prevalence, ranged from 5.0 to 28.6% depending on the cohort studied. Frailty in these studies was associated with increasing age, but was present at younger ages not traditionally associated with frailty, which is mainly seen as a syndrome of ‘old age’. When compared to HIV-negative individuals, HIV increased the likelihood of developing frailty and in those with HIV, increasing age, presence of

comorbidity, an AIDS diagnosis and low current, and possibly nadir CD4+ cell-count were predictors of frailty.

To our knowledge this is the first evaluation of frailty in HIV using systematic review methodology. The strengths of this study include our comprehensive search strategy encompassing multiple electronic databases alongside searches of conference proceedings and target journals in an attempt to ensure that all of the published literature was captured. Additionally our focus on frailty assessment based upon the Fried FP allowed for a degree of standardisation across the studies. Although heterogeneity was still considerable it would have been worsened by inclusion of alternative frailty assessment methods. In spite of recent international attempts there is still no consensus definition of frailty (12,29) but the FP was the most commonly used tool in population-based studies (13).

To contextualise the frailty prevalence in those with HIV, studies in HIV negative populations where the FP has been employed include the US Cardiovascular Health Study of community-dwelling adults aged ≥65 where prevalence was 6.9% (9); The Study of Health, Aging and Retirement in Europe which investigated a younger cohort (50-64) demonstrating prevalence of 4.1%, which increased to 17.1% in those ≥65 (30) and lastly a 2012 systematic review including 15 studies of community-dwelling adults aged ≥65 (n=44,894) showed a prevalence of 9.9% (31). Therefore the prevalence seen in the broadly younger HIV+ population, with highest median age of 57, is comparable to cohorts of community-dwelling adults aged ≥65.

There are some limitations to this systematic review. Firstly, despite a thorough search strategy it is always possible that some articles have been missed. This would be important if these missing studies contradicted the findings presented here; however given the global finding of frailty occurrence and broadly consistent associated factors we feel the impact would be small. Secondly there was a large amount of heterogeneity across the studies both in terms of the populations studied and the interpretation of the FP making comparisons difficult. Thirdly transitions between frailty states was not evaluable in the cross-sectional studies and where measured in longitudinal studies showed movement in and out of frailty, which makes defining its occurrence difficult. Lastly some of the data presented comes from the era before effective ART, so may not reflect the currently largely well-treated cohort, who may have a different ageing trajectory to those diagnosed before its availability.

To expand, the heterogeneity of the populations studied limits our ability to make clear comparisons between all of the studies. The longitudinal cohorts included restricted study populations by solely including MSMs, the IDU experienced or women. Additionally there is a geographical bias as most studies originate from the US and the two non-US studies represented the lowest and second highest frailty prevalence. This may in part be due to a female predominance in the latter compared to the majority male samples elsewhere, as globally frailty appears more prevalent in women than men (10,32). However the study by Terzian (14) had 100% women but lower frailty prevalence than that of Pathai (22) supporting a need to explore geographical differences in relation to frailty in HIV and the many potential confounders such as nutrition, late versus early diagnosis, HIV duration and ART experience. Additionally the majority of studies are based on convenience over random sampling strategies making it difficult to tease out the role of selection bias and

confounding. Most recruited through HIV-clinics and those attending clinics may represent the less-well end of service user spectrum and bias frailty towards overestimation or conversely, the fitter end of the cohort may be more able to attend or be more proactive about their own health leading to underestimation.

With regards the interpretation of the FP, the vast majority used either a frailty related phenotype based on retrospective data or a modified frailty phenotype, all of which, including the original phenotype have not been validated in younger HIV+ cohorts which may affect the accuracy of frailty diagnosis with potential for misclassification. In MACS particularly, frailty may have been underestimated when four rather than five criteria were used, as a trend of reducing frailty prevalence was reversed with the addition of grip strength in 2005 (17). However despite this lack of validation, where the predictive ability of the phenotype in terms of adverse outcomes has been examined this appears consistent with that of traditional elderly cohorts (15,21,27). Additionally using population based cut-offs for phenotypic criteria has been shown to correlate well to original methodology (33). There is however a general criticism of the FP method in that it represents a one-dimensional approach to frailty that focuses too heavily on physical characteristics whilst neglecting broader cognitive, functional and social parameters (34).

This review has identified some important predictors of frailty in individuals with HIV. Most notably is the association with low current CD4+ count, which reflects advanced HIV and stresses the importance of proactive testing to avoid late diagnosis where CD4+ count is by definition lower, the magnitude of CD4 reconstitution on ART is less, and the risk of frailty appears highest. This finding is important as immune dysfunction and the possible association with uncontrolled inflammation has been implicated in the pathophysiology of frailty outside of HIV (11).

This review highlights the key issue of frailty in individuals with HIV, which appears to have prevalence comparable to HIV-negative individuals aged over 65. We have shown that important predictors include increasing age, advanced immunosuppression and the presence of comorbidities. We have stressed the limitations in current work and recommend an ongoing need for further research in this area in the form of well-designed longitudinal cohort studies in mixed populations that reflects the current cohort ageing in the presence of HIV. Future work should ideally be conducted across the lifespan to allow incident frailty and frailty dynamics, particularly pre-frail state, to be assessed along with predictors of transitions such as age, immune thresholds and comorbidity burdens. Though challenging, well-chosen controls will help to unpick the contribution of HIV over other disease and socio-demographic factors to frailty. Lastly longitudinal work will permit us to investigate whether frailty in individuals with HIV is associated with the same adverse outcomes seen in HIV- older adults, which if present should promote clinical and research activity into prevention and/or reversal of frailty.

Total word count: 3498

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Table 1: Characteristics of included studies

First author, year (Country)	Design	Population	Age HIV+ (measure)	% male	N[a]	N HIV+	HIV+ frailty Prevalence % (% pv)[b]	Outcome measure	Frailty criteria
Althoff, 2013 (USA)(17)	Cohort	Multicentre AIDS Cohort (MACS) MSMs >18 years old +/- HIV Urban community Oct 2007-Sept 2011	53.8 frail 50.5 non-frail (median)	100	1946	898	28.6 (12)	Prospective Modified FP. Frail if ≥3/5 criteria	Weakness (grip strength[c]) Slowness (4m timed walk[c]) Self-reported weight loss Self-reported exhaustion[d] Low physical activity[e]
Desquilbet, 2007 (USA)(25)	Cohort	MACS HIV- cohort Apr 1994-Nov 2004 HIV+ cohort Apr 1994-Jan 1996	39 (median)	100	2150	245	13.9 (7.2)	Retrospective FRP Frail if ≥3/4 criteria	Self-reported slowness[f] Self-reported Self-reported exhaustion[d] Low physical activity[e]
Desquilbet, 2009 (USA)(26)	Cohort	MACS HIV+ cohort April 1994-April 2005	45 (median)	100	1046	106	- (5.4)	Retrospective FRP. Frail if ≥3/4 criteria	Self-reported slowness[f] Self-reported Self-reported exhaustion[d] Low physical activity[e]
Desquilbet, 2011 (USA)(27)	Cohort	MACS HIV+ cohort initiating ART pre-2001	43 (median)	100	596	596	13.9	Retrospective FRP. Frail if ≥3/4 criteria	Self-reported slowness[f] Self-reported Self-reported exhaustion[d] Low physical activity[e]
Erlandson, 2012 (USA)(19)	Cross-sectional	HIV+ aged 45-65 on ART University Hospital clinic January 2009-January 2010	50.8 (median)	85	359	359	7.5	Prospective modified FP. Low function (frail) if ≥3/5 criteria	Weakness (grip strength[g]) Slowness (4.5m timed-walk[h]) Self-reported weight loss Self-reported exhaustion[i] Low physical activity[e]
Ianas, 2012 (USA) (20)	Cross-sectional	Convenience sample. HIV+ ≥18 years +/- ART University outpatient clinic May-December 2010	21-78 (range)	74	100	100	19.0	Prospective modified FP. Frail if ≥3/5 criteria	Weakness (grip strength[g]) Slowness (4.5m timed-walk[h]) Self-reported weight loss Self-reported exhaustion[i] Low physical activity[e]
Onen, 2009	Cross-	Convenience sample	41.7	71	445	445	9.0	Prospective modified	Weakness (grip strength[g])

(USA)(21)	sectional	University Hospital clinic HIV+ ≥18 years +/- ART June-December 2008	(mean)					FP. Frail if ≥3/5 criteria	Slowness (4.5m timed-walk[h]) Documented weight loss Self-reported exhaustion[i] Low physical activity[e]
Pathai, 2013 (South Africa) (22)	Case-control	Unselected sample >30 years HIV+ +/-ART Community treatment centre HIV- controls community HIV prevention site May-Dec 2011	41.1 (mean)	27	504	248	19.4	Prospective modified FP. Frail if ≥3/5 criteria	Weakness (grip strength[g]) Slowness (4.5m timed-walk[h]) Documented weight loss Self-reported exhaustion[i] Low physical activity[e]
Piggott, 2013 (USA)(15)	Cohort	AIDS linked to Intravenous experience (ALIVE). History IVDU +/- HIV Community-based cohort From July 2005	48.7 (median)	63	1230	357	14.6	Prospective modified FP. Frail if ≥3/5 criteria	Weakness (grip strength[g]) Slowness (4.5m timed-walk[h]) Documented weight loss Self-reported exhaustion[i] Low physical activity[e]
Sandkovsky, 2013 (USA) (28)	Cross-sectional	Pilot-study Convenience sample University Hospital clinic HIV+ aged 20-40 or >50 years +/- ART	20-70 (range)	71	41	41	17.1	Prospective modified FP. Frail if ≥3/5 criteria	Weakness (grip >1 SD below mean) Slowness (Timed Gait Test >11 secs) Self-reported weight loss Exhaustion (Fatigue Severity Scale score >36) Low activity (POMS activity scale <2)
Terzian, 2009 (USA)(14)	Cross-sectional	Nested within Women's Interagency HIV Study Urban, community cohort of women >13 years +/- HIV. Jan-Dec 2005	41 (median)	100	1781	1206	9.0	Prospective modified FP. Frail if ≥3/5 criteria	Weakness (grip strength) Slowness (4m walk time) Self-reported weight loss Self-reported exhaustion[i] Low physical activity[e].
Abstracts									
Davila-De la Llavre, 2013 (Mexico)(23)	Cross-sectional	Community Study HIV+ aged 50 and over on ART	54 (mean)	80	116	116	5.0	Prospective FP	'Fried phenotype' Individual criteria not specified.
Greene, 2014 (USA) (24)	Cross-sectional	Community Study HIV+ aged 50 years on ART	57 (median)	94	142	142	8.5	Prospective FP	'Fried phenotype' Individual criteria not specified.

a- Total study population
b- frailty prevalence based on person-visits
c- lowest 20% for activity
d- "yes" to "during the past 4 weeks, as a result of your physical health, have you had difficulty
h- Predefined cut-offs based on gender and height
i- Response of 3-4 days per week or most of the time "everything I did was an effort" or "I just could not get going' on the CES-D (Center for Epidemiological Studies Depression) scale.
ART- anti-retroviral therapy

performing your work or other activities?
e- "yes, limited a lot" to the question "Does your health now limit you in vigorous activities?"
f- "yes, limited a lot" to "Does your health now limit you walking several blocks?"
g- Predefined cut-offs based on gender and BMI

FP- frailty phenotype
FRP- frailty related phenotype
IVDU- intravenous drug use
MSM- men who have sex with men

Table 2: Newcastle-Ottawa scale quality evaluation by design type

First author, year	Selection	Comparability	Outcome	Total
Cohort design				
Althoff, 2013 (17)	3	2	3	8
Desquilbet, 2007 (25)	2	2	3	7
Desquilbet, 2009 (26)	2	2	3	7
Desquilbet, 2011 (27)	3	2	2	7
Piggott, 2013 (35)	2	2	2	6
Case-control				
Pathai, 2012 (22)	2	2	3	7
Cross-sectional				
Erlandson, 2012 (19)	2	2	3	7
Ianas, 2012 (20)	2	2	3	7
Onen, 2009 (21)	3	0	3	6
Sandkovsky, 2013 (28)	3	1	2	6
Terzian, 2009 (14)	2	2	3	7
Abstracts- (cross-sectional design)				
Davilla, 2013 (23)	2	0	2	4
Greene, 2014 (24)	2	0	2	4

Figure 1: A funnel-plot to assess publication bias of included studies (utilizing random effects model)

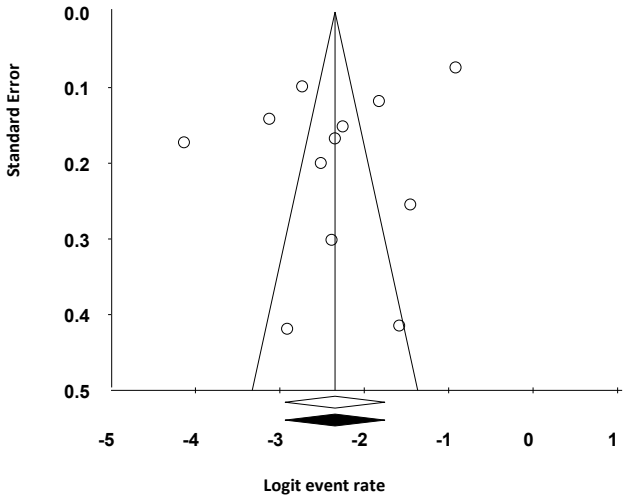

Figure 2: Flow diagram of reviewed studies: