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Non-clinical outcomes of antiretroviral therapy for HIV/AIDS in developing countries: a systematic literature review

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Center for International Health and Development

Boston University

**Non-clinical outcomes of antiretroviral
therapy for HIV/AIDS in developing
countries: a systematic literature review**

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Abstract

The impacts of antiretroviral therapy on quality of life, mental health, labor productivity, and economic wellbeing for people living with HIV/AIDS in developing countries are only beginning to be measured. We conducted a systematic literature review to analyze the effect of antiretroviral therapy (ART) on these non-clinical indicators in developing countries and assess the state of research on these topics. Both qualitative and quantitative studies were included, as were peer-reviewed articles, gray literature, and conference abstracts and presentations. Findings are reported from 12 full-length articles, 7 abstracts, and 1 presentation (representing 16 studies). Compared to HIV-positive patients not yet on treatment, patients on ART reported significant improvements in physical, emotional and mental health and daily function. Work performance improved and absenteeism decreased, with the most dramatic changes occurring in the first three months of treatment and then leveling off. Little research has been done on the impact of ART on household wellbeing, with modest changes in child and family wellbeing within households where adults are receiving ART reported so far. Studies from developing countries have not yet assessed non-clinical outcomes of therapy beyond the first year; therefore, longitudinal outcomes are still unknown. As ART roll out extends throughout high HIV prevalence, low-resource countries and is sustained over years and decades, both positive and adverse non-clinical outcomes need to be empirically measured and qualitatively explored in order to support patient adherence and maximize treatment benefits.

Keywords:

antiretroviral therapy, quality of life, labor productivity, household wellbeing, developing countries

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Introduction

The clinical, immunologic, and virologic effects of antiretroviral therapy (ART) for people living with HIV/AIDS in resource-poor countries are well-documented. For those who adhere to therapy, CD4 counts can rise quickly and viral loads may drop to undetectable levels in the space of a year (Akileswaran, Lurie, Flanigan, & Mayer, 2005; Fairall et al., 2008; Silveira, Draschler Mde, Leite, Pinheiro, & da Silveira, 2002). These improved clinical markers lead to fewer opportunistic infections and overall reductions in AIDS-related morbidity and mortality (Fairall et al., 2008; Sow et al., 2007). What is less clear is the extent to which these improvements in clinical and laboratory outcomes translate into better physical and mental health and socioeconomic wellbeing for patients and their households. These non-clinical outcomes, though secondary to patient survival and reduced morbidity as goals of treatment provision, will become increasingly important as more patients initiate and remain on ART in developing countries. If treatment of AIDS allows patients to resume relatively normal lives—including supporting their families, working productively, and participating in civil society—then the long-term sustainability of large-scale treatment provision will be bolstered. If, on the other hand, quality of life and social and economic wellbeing of ART patients are low, sustaining life-long treatment adherence may be even harder than expected.

While the literature about quality of life and mental health outcomes of ART for HIV/AIDS in North America and Europe is extensive, much less is available from developing countries. Little research on the relationship between ART and workforce participation or labor productivity has been done in either developed or developing country settings. The last several years have, however, seen the publication of systematic reviews of research assessing the impact of ART in developing countries on sexual risk behavior (Crepaz et al., 2004; Kennedy, O'Reilly, Medley, & Sweat, 2007), treatment adherence (Akileswaran et al., 2005; Gill, Hamer, Simon, Thea, & Sabin, 2005; Mills et al., 2006), and patient retention (Rosen, Fox, & Gill, 2007). In this paper, we review reports of the effect of ART on quality of life, labor productivity, and household wellbeing in developing countries and assess the state of research on these topics.

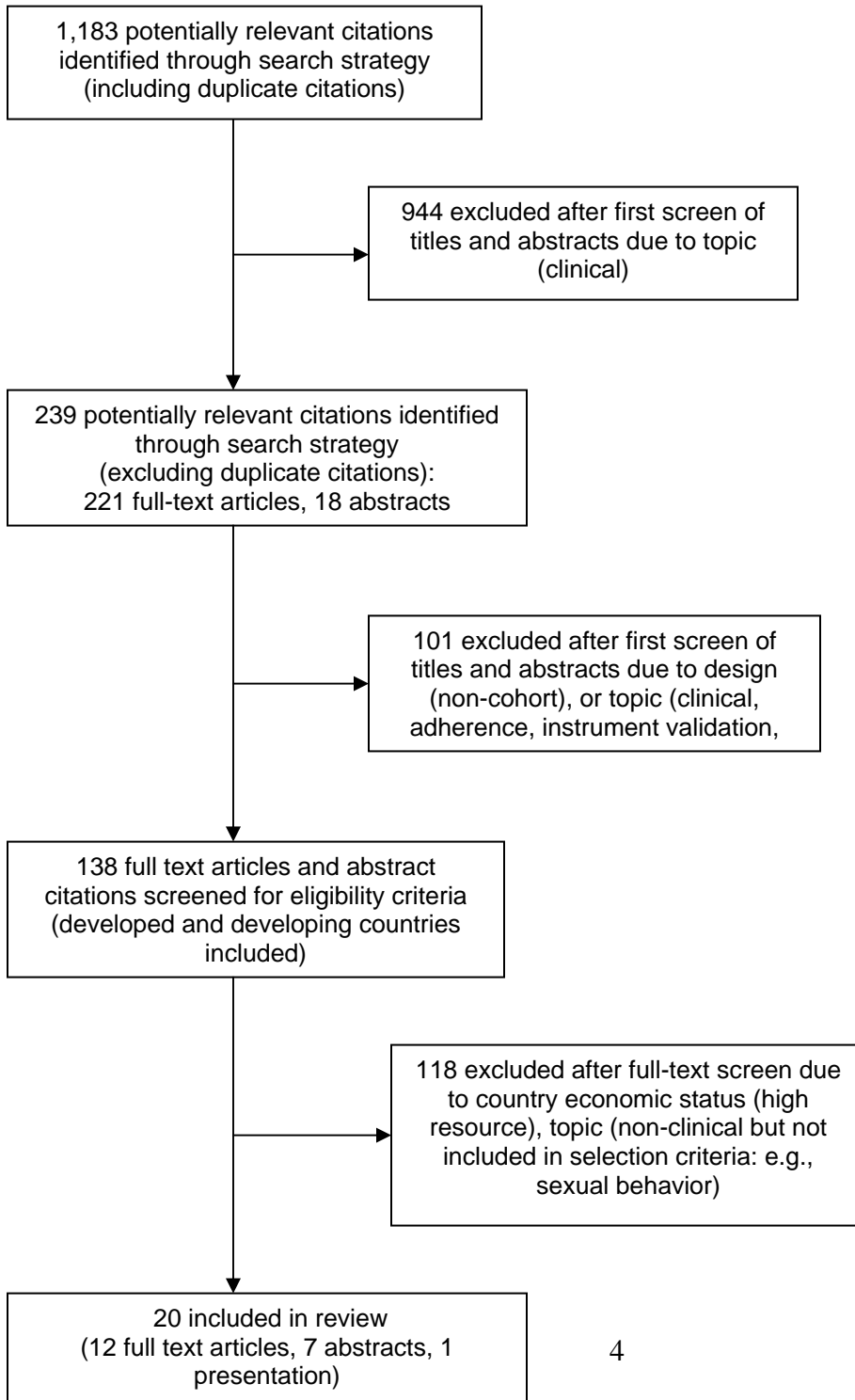
Methods

Using broad search term combinations to capture a wide range of non-clinical outcomes and geographic regions, we conducted a systematic search of the English-language published literature and conference abstracts. We searched Ovid/Medline (1996-September 2008), PubMed (inception to September 2008), Psych Info (inception through September 2008), Web of Science (inception to September 2008), and Google Scholar, pairing the term *antiretroviral therapy* with each of the following: *developing countries, Africa, Asia, Latin America, former Soviet Union/USSR, Russia, Caribbean, Brazil, China, India, Thailand, socioeconomic, mental health, quality of life, work productivity, household welfare, educational/school attainment*. Synonyms (*low resource countries, labor/employment, efficiency/productivity*) were employed according to database-specific preferences, and terms were linked to medical subject headings in Ovid/Medline. Bibliographies of relevant articles were examined, and abstract archives from the International AIDS Society (IAS) conferences (2001-2008) and of the Conference on Retroviruses and Opportunistic Infections (1997-2007) were searched.

Our inclusion criteria required that the publications describe cohorts of adult patients on ART in developing countries; report outcomes related to physical or mental health, labor productivity,

and/or household wellbeing; and compare patients on ART to patients not/not yet on ART or patients on ART at different points of treatment duration. Studies reporting only clinical outcomes or treatment-related behavior (e.g. adherence), limited to instrument validation and modification, or conducted in developed countries were excluded. Eligible studies were identified by the first author (JB) and confirmed by the second and third authors (FF and SR). Findings of the eligible studies were organized by topic and summarized.

Figure 1. Study flow chart



Results

We reviewed 20 publications (12 full-length papers, 7 conference abstracts, 1 presentation) representing 16 studies selected from a total of 1,183 potential relevant citations, as illustrated in Figure 1. All the papers report studies conducted in sub-Saharan Africa. The conference abstracts and presentation extend the geographic range of the review to Asia and Latin America.

Physical, emotional, and mental health outcomes of ART

For the purposes of this review we use the term “quality of life” as defined by Last (2001): “The degree to which persons perceive themselves able to function physically, emotionally, and socially.” This definition captures a broad set of domains and is not limited to any particular instrument or scale, but includes the wide range of measurement approaches used in the literature.

Physical health

Findings describing the impact of ART on physical, emotional, and mental health indicators are summarized in Table 1.

Compared to HIV-positive patients not yet on treatment, patients on ART report significant improvements in physical health. In the Free State Province of South Africa, data has been collected on subjective differences in physical health for patients who have initiated ART, patients who have qualified for treatment but have not yet started, patients taking ART for less than 2 months, and patients taking ART for longer than 4 months (Booyesen, Van Rensburg, Bachmann, Louwagie, & Fairall, 2007; Louwagie et al., 2007). Qualification for treatment alone appeared to boost self-perception of physical health with 55.3% of those awaiting treatment reporting improvements and 86.1% of patients receiving treatment reporting improvement ($p<0.001$). Self-reported improvement in physical outcomes increased over the first three months on treatment and then plateaued. Seventy-seven percent of patients on ART for less than 30 days reported overall health improvement. This proportion reached 85% for those on treatment up to 2 months and stabilized at approximately 90% for those on treatment for 3 months or longer (Booyesen et al., 2007). Within this cohort, Louwagie et al. (2007) report that 94% of those on ART reported no problems with self care compared to 83% awaiting treatment ($p=0.001$).

Physical quality of life was also found to improve over time for ART patients in the Khayelitsha area of Cape Town, South Africa mobility, self-care, ability to perform usual activities, and pain/discomfort were assessed at baseline and after 1, 2, 3, 6, and 12 months on ART (Jelsma, MacLean, Hughes, Tinise, & Darder, 2005). The proportion of patients reporting no problems with self-care increased from 90.5% at baseline to 94.8% at 3 months, and 100% at 12 months ($p=0.031$). This pattern of rapid improvement through month 3, followed by more gradual gains, was similar for usual activities (baseline 75.8%, 3 months 87.6%, 12 months 94%) ($p<0.01$). Pain and discomfort, by contrast, decreased steadily over the full first year of treatment, with 29.5% of patients reporting no problem at baseline, 53.6% at 3 months, and 73.5% at 12 months ($p<0.01$) (Jelsma et al., 2005).

Improvements in physical health over the first year of treatment were also seen in rural Uganda where researchers found significantly improved mean MOS-HIV scores for overall physical health and all domains ($p<0.001$) between baseline and 1 year (Stangl, Wamai, Mermin, Awor,

& Bunnell, 2007). Overall physical summary scores (PHS) in this cohort rose from 39.2 at baseline to 54.2 after 1 year on ART. Role function jumped from 49.7 to 92.8; general health perception from 19.9 to 58.1; bodily pain from 39.4 to 75.4; vitality from 43.5 to 77.0; and physical function from 59.6 to 90.3. In South Africa, patients not on ART were consistently more likely to report body pain or headache, nausea, and fatigue (Rosen, Ketlhapile, Sanne, & DeSilva, 2008).

Emotional and mental health

ART was also associated with improved emotional and mental health for most patients. Just as qualification for and anticipation of receiving treatment appeared to boost perceived improvement in physical health among the Free State cohort, Booysen et al. (2007) found that 65% of patients who had qualified for but not yet initiated ART reported improved emotional wellbeing, while 86.1% of those receiving ART reported improvement ($p < 0.001$). Seventy-nine percent of patients on treatment for less than 30 days reported improved emotional wellbeing. The proportion of those reporting improvement rose to just over 90% in months 2 and 3 and leveled off at 80% after 90 days. The authors interpret this trend of a quick rise in subjective emotional wellbeing in the first couple of months of treatment as a “health effect” that declines over time as the novelty of treatment wears off and is replaced by the reality of life-long treatment adherence. This study also found significant differences between patients on treatment compared to those awaiting treatment in the following domains: satisfaction in personal life, satisfaction with yourself as a person, and fun in life.

In all cohorts, ART was associated with reduced anxiety, depression, and dementia. In Khayelitsha, 85.5% of ART patients reported “no problems” with depression/anxiety after 12 months on ART, from 68.4% at baseline ($p = 0.023$) (Jelsma et al., 2005). In rural Uganda, Stangl et al. (2007) found that mental health summary scores (MHS) improved at the same pace as physical health scores and CD4 counts, increasing from 40.0 at baseline to 54.2 at twelve months ($p < 0.001$). Depression decreased in this cohort from 46% at baseline to 8% after twelve months on ART (p -values not reported) (Bock et al., 2008).

Finally, a small study in Kampala measuring changes in dementia over the first 6 months of treatment found that 61% of the 23 patients surveyed presented with mild dementia at baseline (Memorial Sloan Kettering dementia stage 1) (Sacktor et al., 2006). At 3 months, the proportion with mild dementia fell to 26% and to 4% by 6 months (p -values not reported).

Table 1. Quality of life

Reference	Location	Study design	Sample	Instrument	Key findings
Addo-Atuah et al. (2006) (abstract)	Ghana	Cross-sectional, qualitative study	20 PLWHA receiving ART from 4 public clinics: 35% on ART <1 year 55% on ART 1-2 years 10% on ART >2 years	Open-ended questionnaire	Patient-reported outcomes of ART, not disaggregated by treatment duration Noticeable improvement in health status: 100% Improved function: 100% Working or capable of working: 100% Improved relationships with family and friends: 100%

Reference	Location	Study design	Sample	Instrument	Key findings
					Adverse medication effects: 50% Difficulty accessing food: 15% Increase in hunger sensations after initiating ART: 100%
Bock et al. (2008) (abstract)	Uganda	Prospective cohort followed over 12 months	866 PLWHA on ART, and participating in home-based care project evaluated at baseline and 12 months	CES-D	Patient-reported depression and daily function over 12 months Baseline: 402 (46%) patients reported depression; 435 (50%) reported functional limitations 12 months: prevalence of depression dropped to 8%; prevalence of functional impairment dropped to 7%
Booyesen et al. (2007)	Free State Province, South Africa	Baseline report of prospective cohort study	Index: 268 ART patients Reference: 103 patients awaiting ART	South Africa Quality of Life Trends domains Open-ended questions to capture self-reported improvements	Patient-reported changes in subjective physical and emotional well being: patients qualified for but not yet on ART and patients on treatment from <20 days to >90 days Improvements in physical health since completing drug readiness training: patients on ART 86.1%; awaiting ART 55.3% (p<0.001) Improvements in emotional well-being since completing drug readiness training: patients on ART 86.1%; awaiting ART 80.2% (p<0.001) Satisfaction in personal life: patients on ART 79.9%; awaiting ART 74.7% (p=0.026) Satisfaction with yourself as a person: patients on ART 92.1%; awaiting ART 85.2% (p=0.023) Fun in life: patients on ART 74.9%; awaiting ART 61.3 (p=0.005)
Erhabor et al. (2006) (abstract)	Nigeria	Prospective cohort followed for 48 weeks	Unclear	Questionnaire on adverse clinical events, general health perception, and emotional effect of pill burden	Patient-reported changes between ART initiation (baseline) and 48 weeks on therapy Current positive health perception: baseline 53%; 48 weeks 87.3% Emotional quality of life declined due to ART-related overweight and truncal obesity, adverse clinical events, Steven Johnson's syndrome, and high pill burden.
Hoosen et al. (2006) (abstract)	Sub-Saharan Africa	Prospective cohort followed for 6 months	23 PLWHA with Kaposi's sarcoma enrolled in clinical trial	EORTC QoL questionnaire (QLQ C30)	Patients with Kaposi Sarcoma report on QoL improvements 6 months after starting treatment. Improved function: cognitive (p=0.003) and social (p=0.046)

Reference	Location	Study design	Sample	Instrument	Key findings
Jelsma et al. (2005)	Cape Town, South Africa	Prospective cohort study measuring QoL at 3, 6, and 12 months after ART initiation	117 ART patients	EQ-5D Visual Analog Score (VAS)	<p>Proportion of cohort reporting no problems in domain at baseline and after 12 months on ART</p> <p>Self-care: baseline 90.5%; 12 months 100.0% (p=0.031)</p> <p>Usual activities: baseline 75.8%; 12 months 94.0% (p<0.01)</p> <p>Pain/discomfort: baseline 29.5%; 12 months 73.5% (p<0.01)</p> <p>Anxiety/depression: baseline: 68.4%; 12 months 85.5% (p=0.023)</p> <p>Mean VAS* at baseline and after 12 months on ART</p> <p>Baseline: 61.7 (SD 22.7)</p> <p>12 months: 76.1 (SD 18.5)</p> <p>*Visual Analogue Scale: 0-100 (0=dead, 100 perfect health) (Shmueli, 2005)</p>
Louwagie et al. (2007)	Free State Province, South Africa	Cross-sectional study measuring HRQoL in PLWHA receiving or awaiting ART	Index: 268 patients on ART Reference: 103 patients awaiting ART	EQ-5D VAS scores	<p>Proportion of cohort reporting no problems</p> <p>Mobility: index 81%; reference 71% (p=0.026)</p> <p>Self care: index 94%; reference 83% (p=0.001)</p> <p>Pain/discomfort: index 60%; reference 44% (p=0.022)</p> <p>Mean VAS for patients receiving ART and patients awaiting ART</p> <p>Receiving ART: 66 (SD 20)</p> <p>Awaiting ART: 62 (SD 23)</p>
Rosen et al. (2008)	South Africa	Baseline report from longitudinal cohort study measuring early impact of ART on functional impairment, symptom prevalence, and employment at 3 clinics	427 patients on ART for 1-6 months (208 on ART 1-3 months, 219 on ART 3-6 months) 453 patients receiving pre-ART care	Questions from South African Census, MOS-HIV, and the WHO Performance Questionnaire	<p>Differences in function prior to ART up to 6 months</p> <p>Mean full days of functional impairment: Pre-ART 1.61 (SD 2.01) ART 1-6 months 0.87 (SD 1.65) (p<0.001)</p>
Sacktor et al. (2006)	Kampala, Uganda	Prospective cohort study measuring QoL at baseline, 3, and 6 months after treatment initiation	23 patients from the Infectious Disease Clinic at Mulago Hospital	Memorial Sloan Kettering Dementia Scale Karnofsky Functional Performance Scale	<p>Changes in dementia at baseline, 3 and 6 months</p> <p>Mild dementia: (p=0.046) Baseline: 61% 3 months: 26% 6 months: 4%</p> <p>Mean Karnofsky Score</p> <p>Baseline: 65 3 months: 75* 6 months: 80*</p> <p>*75 indicates ability to care for self but not to work or conduct normal activity</p>

10.81 fewer days than comparison men ($p=0.00$), and by the fourth month of treatment had rebounded to the point where differences in days spent plucking between the two groups were no longer significant (Larson et al., 2008).

Female tea pluckers did not rebound as successfully as their male counterparts. Women in the intervention group plucked tea significantly fewer days than female comparisons in each of the 12 months prior to treatment as well as in the months after starting ART (Larson et al., 2008). At treatment initiation, intervention women plucked tea 14.82 fewer days than comparison women ($p=0.00$). After twelve months of treatment, that difference had fallen to 6.36 fewer days plucking than comparison women ($p=0.00$). Despite this positive trend, intervention women still plucked approximately 30% fewer days than comparison women by the end of the first year on treatment.

In Botswana, no difference in absenteeism was found between diamond mind employees who ultimately enrolled in the company's AIDS treatment program and the workforce as a whole in the 5 years to 15 months prior to treatment, but absenteeism rose sharply in the last year before treatment initiation, to a high of 5 days absent in the month before initiation. Once treatment started, absenteeism fell equally sharply, so that after an average of 6 months on treatment, enrolled workers' attendance returned to a pattern similar to the rest of the workforce (Habyarimana, Mbakile, & Pop-Eleches, 2008).

In South Africa, a similar pattern was discerned among Anglo American mining group employees receiving ART; 7.5 days of work were missed per month at treatment initiation, 2.9 days after 6 months, and 2.1 after 18 months (comparison data not provided) (Charalambous et al., 2007; Muirhead et al., 2006). Also in South Africa, workers on ART from 1-2 months reported a significant difference in mean days of work missed in the previous month (4.2), compared to those on ART for 3-6 months (1.3) (Rosen et al., 2008). In India, significant improvements in ability to work and hours worked occurred in the first 6 months of treatment and were sustained over the following year, with no significant changes at 12 or 18 months (Thirumurthy et al., 2008).

Thirumurthy, Graff Ziven, and Goldstein (2005) measured labor force participation in Kenya in 266 HIV-positive adults on ART against a random sample of 503 comparisons in two interviews over a period of 6 months, categorizing patients as "on ART for 100 days or less" and on "ART 100 days or more." They found that patients on treatment for longer than 100 days at baseline worked more than those just starting treatment, but significant improvement in ability to work was found in those on treatment for 3 months or less. Patients who had been on ART for less than 100 days at baseline participated in the labor force 28.2% less than comparisons at that point in time and 12.8% less than comparisons at month 6. This gap in labor force participation narrowed for patients on ART for 100 days or longer who worked 7.9% less than comparisons (Thirumurthy, Graff Zivin, & Goldstein, 2005).

Work performance

Work productivity and performance appear to improve as a result of ART. Prior to beginning treatment, only 12.5% of Cote d'Ivoire Electricity Company workers were able to perform full

duties (Eholie & Nolan, 2003). After 1 year on ART this proportion increased to 84% and to 91% by 2 years (p-values not reported).

In Kenya, productivity differences between HIV-positive male employees and matched comparisons were significant in months 20, 7, 4, and 2 prior to treatment initiation and during the first month of treatment. Once on treatment, there was no significant difference in the amount of tea leaf plucked by male intervention workers. Intervention women plucked significantly less tea 10 out of the total 37 months analyzed compared to intervention men (5/37 months). The data do not reveal the reasons for the differences between the work patterns for HIV-positive men and women. The researchers hypothesize that women may experience more HIV-related sickness both before and after treatment initiation and as a result request more days of light duty. Women known to be HIV-positive, they speculate, may simply be assigned to light duty by the clinical officers overseeing their care (Larson et al., 2008).

Work performance trends among HIV-positive employees have also been measured in terms of functional impairment. In South Africa, Rosen et al. (2008) report that patients not on ART were almost twice as likely to report whole or partial days of impairment in the previous week. Employees not on ART reported 1.61 mean full days of functional impairment compared to 0.87 days among those who had been on ART for 1-6 months ($p < 0.0001$).

The most dramatic improvements in ability to work and performance were reported in the first 3 months of treatment. In Kenya, Thirumurthy et al. (2005) found that the largest increases in labor force participation were reported by those who had been on treatment 100 days or less at baseline. Six months later (6-9 months after treatment initiation) their labor force participation increased by 16.7% and hours worked increased by 6.934_{per week}. Workers who had been on ART longer than 100 days at baseline had much smaller increases in work participation (1.3%) and hours worked (0.992) (Thirumurthy et al., 2005).

Table 2. Labor productivity (workplace)

Reference	Location	Design	Sample	Key findings
Eholie and Nolan (2003)	Cote d'Ivoire	Prospective cohort study measuring socioeconomic impact of private enterprise ART program over 3 years	HIV+ employees of Electricity Company of Cote d'Ivoire	<p>Counts of HIV+ employees, employees on ART, HIV-related deaths, proportion able to perform full duties, and mean sick leave (p-values not reported)</p> <p>1999 (n=3459): 96 HIV+ workers; 0 on ART; 16 HIV-related deaths; 12.5% of workers able to perform full duties; mean 3.5 months sick leave</p> <p>2000 (n=3482): 94 HIV+ workers; 62 on ART; 9 HIV-related deaths; 84% workers able to perform full duties; mean 0.24 months sick leave</p> <p>2001 (n=3728): 101 HIV+ workers; 74 on ART; 5 HIV-related deaths; 91% of workers able to perform full</p>

				duties; mean 0.16 months sick leave
Habyarimana et al. (2008)	Botswana	Retrospective cohort assessing impact of ART on worker absenteeism up to five years after ART initiation	441 workers from 2 Debswana Diamond Company mines receiving ART Comparison population of approximately 7,000 workers not enrolled in treatment program (HIV status unknown)	Absenteeism in days/month for employees on ART v. rest of workforce 5 years to 15 months before ART initiation: no difference between enrolled workers and rest of workforce Last year before initiation: absenteeism of enrolled workers increases sharply to a peak of 5 days/month in last month First 6 months after initiation: absenteeism declines sharply 7 months-4 years after initiation: no difference between enrolled workers and rest of workforce
Iro et al. (2008) (abstract)	Nigeria	Prospective cohort assessing effect of ART on work productivity	124 HIV+ patients on ART 111 HIV+ patients not yet on ART 124 HIV- or unknown serostatus individuals	Mean work days lost (p<0.05): HIV+ on ART: M=1.06 (SD 1.516) HIV+ not on ART: M=4.16 (SD 3.282) HIV- or unknown serostatus: M=0.05 (SD 0.366) Mean restricted activity days and bed disability days: Differences between HIV+ patients on ART reported to be significantly fewer than patients not on ART. Specific numbers not reported.
Larson et al. (2008)	Kericho District, Kenya	Retrospective cohort assessing early effects of ART on tea plucker presenteeism and productivity over 37 months	59 intervention tea plantation employees on ART 1992 comparison workers matched by work units (HIV status unknown)	Mean days spent plucking 24 months preceeding and 12 months after ART initiation 24 months prior to ART: intervention 16.41; comparison 17.05 (p=0.59) 1 month prior to ART: intervention 13.68; comparison 18.77 (p<0.00) 12 months on ART: intervention 14.38; comparison 17.05 (p=0.04)
Larson et al. (2008)	Kericho District, Kenya	Retrospective cohort assessing early effects of ART on tea plucker productivity and presenteeism over 37 months	59 intervention tea plantation workers on ART 1992 comparison workers matched by work units (HIV status unknown)	Gender disaggregated mean days plucking and mean kgs of tea leaf harvested per month 24 months prior to ART: Mean days plucking: male intervention 17.35; male comparison 16.90 (p=0.85);

				<p>female intervention 15.67; female comparison 18.12 (p=0.09)</p> <p>Mean kgs of tea leaf plucked: male intervention 37.97; male comparison 42.23 (p=0.11); female intervention 32.44; female comparison 38.53 (p=0.02)</p> <p>1 month prior to ART: Mean days plucking: male intervention 15.85; male comparison 18.20 (p=0.27) female intervention 11.97; female reference 19.85 (p=0.000)</p> <p>Mean kgs of tea leaf plucked: male intervention 41.26; male comparison 44.59 (p=0.33); female intervention 29.59; female comparison 32.96 (p=0.16)</p> <p>12 months on ART: Mean days plucking: male intervention 14.96; male comparison 15.99 (p=0.67); female intervention 13.91; female comparison 20.26 (p=0.00)</p> <p>Mean kgs of tea leaf plucked: male intervention 35.37; male comparison 36.42 (p=0.76); female intervention 28.67; female comparison 34.15 (p=0.02)</p>
Muirhead et al. (2006) (abstract)	South Africa	Prospective cohort over 3 years	2400 employees of large South African employer	<p>Mean worker absence over 18 months on ART</p> <p>Immediately prior to ART initiation: 7.5 days/month</p> <p>6 months on ART: 2.9 days/month</p> <p>12 months: 2.2 days/month</p> <p>18 months: 2.1 days/month</p>
Rosen et al. (2008)	South Africa	Baseline report from longitudinal cohort study measuring early impact of ART on functional impairment, symptom prevalence, and employment at 3 clinics	<p>427 patients on ART for 1-6 months (208 on ART 1-3 months, 219 on ART 3-6 months)</p> <p>453 patients receiving pre-ART care</p>	<p>Differences in absenteeism prior to ART up to 6 months</p> <p>Mean days absent due to health in previous month: Pre-ART 3.1 (SD 7.5); ART 1-6 months 2.7 (SD 7.7) (p=0.0108)</p> <p>ART 1-3 months 4.2 (SD 9.8) ART 3-6 months 1.3 (SD 5.0) (p=0.0353)</p>
Sgombich et al. (2006) (abstract)	Chile	Prospective cohort	<p>Baseline: 799 PLWHA receiving ART from 8 public hospitals</p> <p>28 months: 512 PLWHA followed up</p>	<p>HIV+ worker absenteeism over 28 months on ART</p> <p>Days absent decreased from 78 days/year to 52 days/year (p=0.0372) between baseline</p>

<p>Thirumurthy et al. (2005)</p>	<p>Kosirai District, Kenya</p>	<p>Prospective cohort assessing labor supply of ART patients at baseline and 6 months</p>	<p>191 ART patients and 1286 randomly sampled comparison adults</p>	<p>and 28 months</p> <p>Labor force participation and hours worked in last week at baseline (Round 1) and at a 6 months (Round 2)</p> <p>Baseline: Illness reported as reason for not working in past week: ARV patients 85% Comparisons 8%</p> <p>Patients on ART for less than 100 days at baseline: worked 28.2% less than comparisons in Round 1 and 12.8% less in Round 2 (p=0.01); worked 15.785 less hours than comparisons at baseline and 9.916 fewer hours in Round 2 (p=0.01)</p> <p>Patients on ART for more than 100 days at baseline: worked 7.9% less than comparisons in Round 1 and 7.1% less in Round 2 (p=0.05); worked 8.2 days less than comparisons at baseline and 8.133 less in Round 2 (p=0.01)</p>
<p>Thirumurthy et al. (2008) (conference presentation)</p>	<p>Tamil Nadu, India</p>	<p>Prospective cohort following patients on ART over 18 months</p>	<p>Patients enrolled in Tamil Nadu Family Care Continuum Program</p> <p>515 patients receiving ART</p> <p>804 comparison patients (HIV+ but not yet eligible for ART)</p>	<p>Changes in labor force participation, hours worked in past week, and income in past 30 days</p> <p>Baseline: 31% worked in past week; 12.7 hours worked in past week; 710.7 rupees earned in past 30 days</p> <p>6 months on ART; 53% worked in past week 25.5 hours worked in last week; 1135.3 rupees earned in past 30 days</p> <p>12 months on ART: 60.5 hours worked in past 29.93 hours worked in past week; 1285.3 rupees earned in past 30 days</p> <p>18 months on ART 58.8 hours worked in past week 26.74 hours worked in last week; 1461.6 rupees earned in past 30 days</p> <p>Differences between baseline and subsequent months significant (p=0.01)</p>

				Differences between months 6, 12, and 18 not significant Findings for comparison group not provided
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Household wellbeing

Data describing the association between an adult’s improved ability to work and child labor, school enrollment, family nutrition (summarized in Table 3) come from cohorts in Kenya and India (Graff Zivin, Thirumurthy, & Goldstein, 2007; H. Thirumurthy et al., 2005; Thirumurthy et al., 2008). In households where the adult on ART had been on treatment for more than 100 days at baseline, boys age 8-12 were found to engage in work outside the house 22.7% (8.644 hours) less 6 months later (Thirumurthy et al., 2005). In households with 2 adult ART patients, labor participation dropped 79.2% (p=0.01) for boys age 8-12 after adults started therapy and 26.7% (p=0.10) for boys age 12-18. However, girls of any age and children in households with only 1 adult on treatment did not experience significant changes. Families with an adult on ART also borrowed significantly less money after 6 months on treatment (Thirumurthy et al., 2008).

Households reported increased consumption of bananas, carrots, beans, and potatoes, within the first 6 months of treatment (Thirumurthy et al., 2008). Wasting in children under age 5 decreased from 12% at baseline to 5% after an adult caretaker had been on ART for 6 months (Graff Zivin et al., 2007). At baseline, children in households with an adult on ART had a significantly higher prevalence of wasting compared to children in a random sample of non-patient households, but this difference virtually disappeared after 6 months on ART.

Finally, treatment of an adult caretaker was also associated with differences in school attendance among children. In the 6 months between baseline and follow up, school enrollment did not change significantly for children living in ART households. But, for children living in households where an adult had just started treatment, the number of hours attended increased by 6.393 hours per week (21%) (Graff Zivin et al., 2007).

Table 3. Household wellbeing

Reference	Location	Design	Sample	Key findings
Graff Zivin et al. (2007)	Kosirai Division, Kenya	Prospective cohort measuring impact of ART on schooling and nutrition of children within household	ART households: 128 children Random sample of households: 352 children	Wasting in children under 5 at baseline and 6 months in ART and random sample households Baseline: ART households 12%; Random sample 4% (p=0.03) 6 months: ART households 5%; Random sample 2% (p=0.17) Increases in number of hours child living with an adult on ART attended school 6 months after baseline <100 days (p=0.05): All children 6.393;

				Boys 8.673; Girls 6.513 >100 days: All children 1.893; (not statistically significant) Boys 4.902 (p=0.10); Girls -1.035 (not statistically significant)
Thirumurthy et al. (2005)	Kosirai Division, Kenya	Retrospective cohort assessing labor supply of ART patients and labor supply of other adults and children in household at baseline and 6 months	Index households: 266 with at least ART patient Comparison households: 503 randomly sampled from district	Proportion of children who worked outside the home in previous week in ART and comparison households at baseline and 6 months Baseline: Boys 8-18: index 74%; comparison 78% (p=0.24) Girls 8-18: index 63%; comparison 74% (p=0.02) 6 months: Boys 8-12 living with adults on ART >100 days worked 22.7 percent less than in Round 1 (p=0.05) Labor differences between rounds were not significant for older boys or girls of any age.
Thirumurthy et al. (2008) (conference presentation)	Tamil Nadu, India	Prospective cohort following patients on ART over 18 months	Patients enrolled in Tamil Nadu Family Care Continuum Program 515 patients receiving ART 804 comparison patients (HIV+ but not yet eligible for ART)	Proportion of families with an adult on ART consuming food items (estimates, p values not reported) Baseline: Bananas 70% Beans 70% Carrots 78% Potatoes 77% 6 months: Bananas 79% Beans 82% Carrots 85% Potatoes 83% 12 months: Bananas 83% Beans 82% Carrots 85% Potatoes 85% 18 months: Bananas 83% Beans 83% Carrots 86% Potatoes 85% Rupees borrowed by families with adult on ART (estimates, p values not reported) Baseline: 11,800 rupees 6 months: 5,000 rupees 12 months: 5,500 rupees 18 months: 5,500 rupees

				Findings for comparison group not provided
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Discussion

For the most part, research on the non-clinical outcomes of antiretroviral therapy in developed, transitional, and developing countries presents positive findings. Those patients for whom treatment is successful, who are able to adhere to drug regimens over time, report improvements in physical, emotional, and mental health, and to some extent their ability to work outside the home, as well as more general improvements in household wellbeing. For those able to remain employed while ill and through treatment initiation, the ability to work improved within 6 months, and levels of absenteeism decreased rapidly.

Maintaining high levels of adherence over the possible decades that ART can extend life will remain challenging for both patients and those providing therapy. The difficulty of sustaining improvements over long periods of time found in developed countries is likely to influence quality of life and adherence in low resource contexts as well (Burgoyne & Renwick, 2004; Burgoyne & Tan, 2008; Gill et al., 2005). Based on the findings we reviewed, physical and mental health improvements seem to stabilize after 6 months. As years on treatment accumulate, researchers will need to track the transition from the buoyancy of treatment optimism to the doldrums of treatment fatigue when the promises of ART are checked by the reality of life with an infectious, sexually transmitted, chronic disease (Addo-Atuah et al., 2006; Carr, 2002; Gray & Berger, 2007; Kumarasamy et al., 2008; Russell et al., 2007).

Our review has several limitations. Because we set out to provide a broad overview of non-clinical research, we have not probed the methods or findings of the studies reported in depth. Finally, the relatively small number of studies found and reviewed, most of which are limited to sub-Saharan Africa, indicates the overall limitations within the non-clinical outcomes field of inquiry. Of equal concern is the relative lack of attention to patients lost to follow up as a result of treatment discontinuation, possibly resulting from adverse outcomes (Rosen, Fox, & Gill, 2007). In terms of the overall state of research on the topic of nonclinical outcomes of ART, the extent to which publication bias is a factor limiting the reporting of adverse outcomes is unknown.

Future research priorities should include continued longitudinal research of ART outcomes beyond 12 months; qualitative exploration of experiences and perceptions of ART patients regarding drug side-effects, continued impairment, treatment fatigue, the so-called “Lazarus phenomenon” resulting from the ability of ART to pull patients back from the brink of death after they have made peace with that fate (Brashers et al., 1999; Thompson & Thompson, 2003), the economic wellbeing of families and households, and more. Full reporting of both positive and negative treatment outcomes should be prioritized in order to understand the specific challenges faced by ART patients in developing countries, support adherence for life, and assist them in maximizing treatment benefits.

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