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Effectiveness of HIV Anti-retroviral Agents on the HIV/AIDS Epidemic

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aims: The scale up of HAART globally has shifted the mortality time table, decreased viral transmission and improved health related quality of life for patients while emphasizing the importance of adherence to therapy for improved outcomes.
Study Design: Review Article.
Place and Duration of Study: Department of Medicine SABA University School of Medicine.
Methodology: Using Pubmed and Science Direct, research was executed from January 2015 to March 2015. Articles used were limited to a study completion date of less than five years. The type of studies used were case control, cohort, cross sectional, follow up, and qualitative studies on human subjects. All studies originated within the last 20 years but to keep the issue current and relevant, preference was given to studies published within the last five years.
Results: The scale up of HAART correlated with a decrease in mortality rates and a lengthening of the death time table. Health Related Quality of Life significantly improved with therapy. Both vertical and horizontal transmission rates showed improvements with the increase of available therapy. Stigma is still a limiting factor to adherence, limiting the gains of HAART.

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Conclusion: HAART has had an overall positive effect in improving the quality of life of patients suffering from the HIV epidemic while working to combat new infections. Causation can be inferred for some aspects as there is adequate literature while certain topics such as stigma need more research.

Ultramini Abstract: HAART has overall improved quality of life for patients while decreasing the mortality time table. It has shifted the perception of HIV from a death sentence to a treatable and preventable diagnosis. Vertical and horizontal transmission have seen great improvements. However, much work has to be done to combat stigma, increase adherence, and decrease attrition to increase the gains of HAART and its effects on the HIV epidemic.

Keywords: HIV; AIDS; HAART; health related quality of life; vertical; horizontal; transmission; stigma; adherence; mortality.

1. INTRODUCTION

Human immunodeficiency virus (HIV), infects the effector cells of human immune system. This leads to a progressive deterioration of the body's defenses, compromising the host's ability to prevent other infections and diseases. According to the World Health Organization (WHO), approximately 35 million people are living with HIV globally, with an approximate rate of two million new infections per year [1]. When the host has experienced more than 20 opportunistic infections and or cancer events, this late stage is referred to as Acquired Immunodeficiency Syndrome (AIDS) [1]. AIDS related causes have killed over 40 million people globally, making HIV the world's leading infectious killer [1].

One way to combat the progression from HIV to AIDS has been through the implementation of Highly Active Antiretroviral Therapy (HAART) [2]. The goal of HAART is to decrease the rate at which HIV can replicate, allowing the body's immune cells to live longer and thus protect the body from other possible infections [2]. In 2013, approximately 12 million people in low or middle income communities had access to HAART [1]. Before HAART was introduced, HIV disease progression and death were mainly determined by the age of seroconversion of the patient and the duration of the infection [1]. Consequently after 1996, the year in which HAART was introduced and widely utilized, large decreases in the rate of progression to AIDS and related mortality causes were seen in the upcoming years [1]. This shifted the normal HIV to AIDS to AIDS related death paradigm [1].

The use of HAART in HIV infected patients has had positive impacts on many aspects of patients' lives and the communities they reside. These include but are not limited to mortality, quality of life outcomes, vertical and horizontal transmission risks, and stigma and discrimination [3].

The expansion of HAART is not only allowing patients to live longer because of a stronger immune system but also allowing patients to recover or even flourish after receiving a distressing diagnosis [1]. Although a decrease in viral load and mortality decreases are key endpoints in many studies, with an increase in lifespan, health related quality of live (HRQoL) is fast becoming a key focus. HRQoL seeks to include not biomedical perspectives and effects of HAART treatment [4,3,5]. With the increase in lifespan, more studies are also assessing factors such as vertical and horizontal transmission risks and their effects on the overall communities' risk of new infections [6,7]. Another important factor, stigma and discrimination and its effects on patients is measured through the both the qualitative lens of adherence and the subjective lens of self-perception and attitudes towards HAART [8,9].

2. METHODOLOGY

Using Pubmed and Science Direct, research was performed from January 2015 to March 2015. Articles used were limited to a study completion date of less than five years. MeSH terms used were "HAART", "HIV", "AIDS", "MEDICATION EFFECTS", "TREATMENT", "SURVIVAL" and "EPIDEMIC". Terms such as "Mortality", "Transmission", "Vertical", "Horizontal", "Stigma", "Discrimination, "Adherence", "Quality of Life", and "HRQoL" were used to narrow down the field of studies to the individual subtopics to be addressed. The type of studies used were case control, cohort, cross sectional, follow up, and qualitative studies.

Animal studies were not required since there was a large number of human studies available on

the topic. All articles used were available in either English or English translation. Access to articles was provided by Hofstra University Library in Hempstead, NY and the Howard University School of Law Library in Washington, D.C. All studies originated within the last 20 years but to keep the issue current and relevant, preference was given to studies published within the last five years. After narrowing down the search 27 studies were selected to give the best overall representation of the topic. The subtopics analyzed were mortality, health related quality of life, vertical viral transmission, horizontal viral transmission, and stigma and discrimination associated with HAART.

3. RESULTS

3.1 Mortality Rates

Electronic data logged my Médecins Sans Frontières of adults aged 16 or older who started HAART between March 2001 and September 2011 from 25 sites across 8 countries in Africa and Asia was analyzed in a multicohort study to assess temporal trends in mortality [1]. A total of 132,334 patients data yielded 299,658 years of follow up with an average of 1.75 years per patient [1]. HAART was started at a median age of 35 with 69% of individuals having a CD4 count of less than 200/microliter while less than 5% had a CD4 count greater than 350 cells/ microliter [1]. On average, 25% of the patients were designated as having a clinical diagnoses of stage 4 disease at initiation [1].

The number of individuals initiating HAART increased dramatically from 4427 in 2001-2003 to 22,863 in 2010 [1]. The average CD4 cell count of patient's newly initiating therapy increased from 97 cells/microliter in 2003 to 184 cells/microliter in 2011 [1]. This includes 30% of patients annually who started HAART with CD4 counts of less than 100 cells/ microliter [1]. Over time the percentage of patients who enrolled with clinical stage 4 disease reduced from 44% to 14% [1].

Over the study period mortality decreased from 17% to 5% at one year and from 22% to 9% at 3 years [1]. From the 25 sites, larger sites with greater expansion had lower mortality rates [1]. After adjusting for size and program expansion rate, with each successive year of enrollment, the risk for death decreased for the 0-12 month time frame and up to 2007 [1]. Larger program size was associated with decreased early mortality (Adjusted hazard ratio (*aHR*) = 0.49, 95% CI: 0.31 to 0.77, for greater than 20,000 vs. less than 500 patients) [1]. The strongest association with death was advanced clinical stage and decreased CD4 count, with the strongest associations for early mortality [1].

In a cohort study, Cornell, M et al explored outcomes after transfer out (TFO) and loss to follow up (LTF) of patients on HAART across four large groups in South Africa [10]. Compared against those patients which were retained, the mortality risk was three times greater amongst TFO patients (*aHR* = 3.11; 95% CI: 2.42 - 3.99) and 20 times higher with LTF patients (aHR = 22.03; 95% CI: 20.02 – 24.21) [10].

In another study in South Africa, Cornell, M et al explored gender inequalities amongst mortality [11]. At the start of ART men had a higher median age vs woman (38 vs. 38 years old) and a lower starting CD4 cell count (85 vs 110 cells/microliter) [11]. Men were also more likely to have started HAART with a CD4 count of less than 50 cells/ microliter (34% vs 26%) and classified as Stage 3 or 4 disease by the World Health Organization [11]. After adjustment men had a 31% higher death risk than woman (aHR = 1.31; 95% CI: 1.22 - 1.41) [11].

3.2 Health Related Quality of Life (HRQoL)

In a cross sectional secondary analytical study conducted in Cape Town, South Africa by Nglazi, M et al, 903 HIV positive individuals greater than the age of 18 were divided on the basis of receiving HAART for greater than 6 months or not receiving HAART at all [3]. 435 were HAART naïve (76% female) and 468 were on HAART (78% female) (15). HRQoL was evaluated using validated EQ-5D (5 domains) and Visual Analogue Scale (VAS) (Table 1) [3]. The five domains assessed in the questionnaire included mobility, self-care, usual activities, pain and discomfort, and anxiety and depression [3]. A score from 0 (worst) to 100 (best) is assessed for healthcare state on the EQ-5D VAS [3]. The HAART Naïve group had a median VAS of 80 (IQR 70-90) vs the HAART group with a score of 90 (IQR 80-100; P<.00001) [3].

In the CAPRISA 002 acute infection study by Tomita, A et al, 51 South African women, with a mean age of 25.9 years (range 18-43), had a baseline CD4 count of 488 cells/mm3 (range 299-1,358) and a viral load of 4.7 copies/ml (IQR

4.2-5.1) at enrollment [5]. The percentage of the cohort that met meaning full improvements in their HRQoL in physical well-being, emotional well -being, functional and global well -being, social well-being, and cognitive function were 39, 30, 20, 36 and 32% respectively [5]. Adjusted linear regression models showed that HAART was associated with higher levels of general HRQoL (b = 12.31, p\0.01), of PWB (b = 2.73, p = 0.03), EWB (b = 2.72, p = 0.03), and SWB sub-domains (b = 3.81, p\0.01) [5]. Stable vs multiple partnership was also a positive indicator of various aspects of HRQoL [overall (b = 14.13, p = 0.03), PWB (b = 6.20, p = 0.01), FGWB (b = 4.28, p = 0.03) and CF (b = 1.88, p = 0.04)] [5].

In a 12 month follow up study in Burkina Faso, 344 patients recorded baseline physical (PHS) and mental health scores (MHS) (Table 2) [4]. The average PHS score increased from 45.4 (standard deviation (SD): 11.1) at baseline to 60 (SD: 3.1) after one year (*P* < 10-4) and the average MHS score also increased from 42.2 (SD: 8.7) to 43.9 (SD: 3.4) (*P* < 10-2) [4]. Patients who suffered on average two symptoms during follow up in the one year period also had higher PHS (63.9) and MHS (43.8) compared to the PHS 68.2 (*P* < 10-4) and MHS 45.3 (*P* < 10-3) of those patients who suffered no symptoms in follow up [4].

3.3 Vertical Transmission Rate

One way to measure the effectiveness of HAART on the HIV epidemic is to compare the rate of vertical transmission between mother and child in HIV positive patients on therapy versus patients who are not receiving any therapy [6]. In a study undertaken by Okafor, I et al. at Enugu State University Teaching Hospital in Nigeria, 188 women tested positive for HIV and were enrolled in preventative mother to child transmission (PMTCT) therapy [6]. Three patients were lost to follow up and two were transferred to other facilities for PMTCT on request [6]. Out of the remaining 183 women that gave birth, one had a set of twins yielding 184 possible infant exposures [6]. Two babies were stillborn and their HIV status was unknown [6]. Testing for HIV status at 6 weeks yielded 182/182 negative results [6]. Four babies were further lost before 18 months to acute illnesses [6]. At 18 months, the remaining 178 infants tested negative for HIV [6].

In a study conducted in Burkina Faso to evaluate the efficacy of HAART therapy in preventing vertical transmission of HIV, HAART was assessed against the New Prophylactic Protocol (NPP) of AZT + 3TC + NVP [12]. The prevalence of HIV infection in infants whose mothers were on HAART during pregnancy was 0.0% (0/114) vs. 6.8% (18/264) for patients who were only administered only the NPP (*P* < .01) [12].

In a study conducted in the Dominican Republic by Lorenzo, O et al., the efficacy of HAART on vertical transmission was measured against the change in recommendation of guidelines issued by the Ministry of Health [13]. The new guidelines after 2008 suggested that all mothers who are HIV positive start HAART to prevent mother to child transmission (MTCT), regardless of evidence of immunodeficiency, whereas following the older guidelines the majority of patients on HAART prenatally had CD4+ counts less than 250 [13].

The study assessed data collected 1274 infants from 34 centers from 1999-2008 and from 302 patients across 18 centers from 2009-2011 [13] (Table 3). Overall HIV infection was diagnosed in 154/1576 infants assessed (9.8%) for time period [13]. However, there was a sharp decline in the proportion infected from 1999-2008 from 11.1% (142/1,274) to 4.0% (12/302) in 2009-2011 (*P* < .001) [13]. The MTCT rate was also found to be higher in those mothers that received a single dose of nevirapine versus those received prenatal HAART therapy for both the 1999-2008 and 2009-2011 time period (6.4% vs. 2.5% and 5.7% vs. 2.9% respectfully) [13]. This difference was only significant statistically when the two time periods were combined with 9/331 (2.7%) of infants infected whose mothers received prenatal HAARTvs. 35/601 (5.8%) of mothers who received a single dose of nevirapine (P = .03) [13]. The duration of HAART was also found to be shorter in those mothers whose infants were HIV positive (median = 16.5 days) vs. those infants who were HIV negative (median = 161 days, *P* = .003) [13]. For the 2009-2011 time period the MTCT rate also varied significantly by the method of delivery with 6.8% for cesarean section to 23.9% for vaginal delivery [13].

3.4 Population Coverage and Horizontal Transmission Risk

Using data from one of Africa's largest population based prospective cohort studies conducted in Hlabisa subdistrict in rural KwaZulu-Natal, South Africa, Tanser, F et al, followed 16,667 subjects who were initially HIV negative, observing

individual seroconversions from 2004 to 2011 [7]. The individual level outcome, time to seroconversion, is regressed against the aggregate level of HAART coverage in the community surrounding the individual [7]. Using data from the African Centre geographic information system, HAART coverage and HIV prevalence around each of the 16,667 individuals was measured by using a two dimensional Gaussian kernel of 3 km search area for each year from 2004 to 2011 (Fig. 1) [7]. The kernel measured HIV prevalence using the data of approximately 10,000 residents who had consented to HIV testing [7]. This prevalence and geographic data is then used to calculate the number of HIV infected individuals within each cell on the grid and subsequently within proximity to each of our subjects [7]. A similar method is used to calculate the density of HAART coverage surrounding each subject [7].

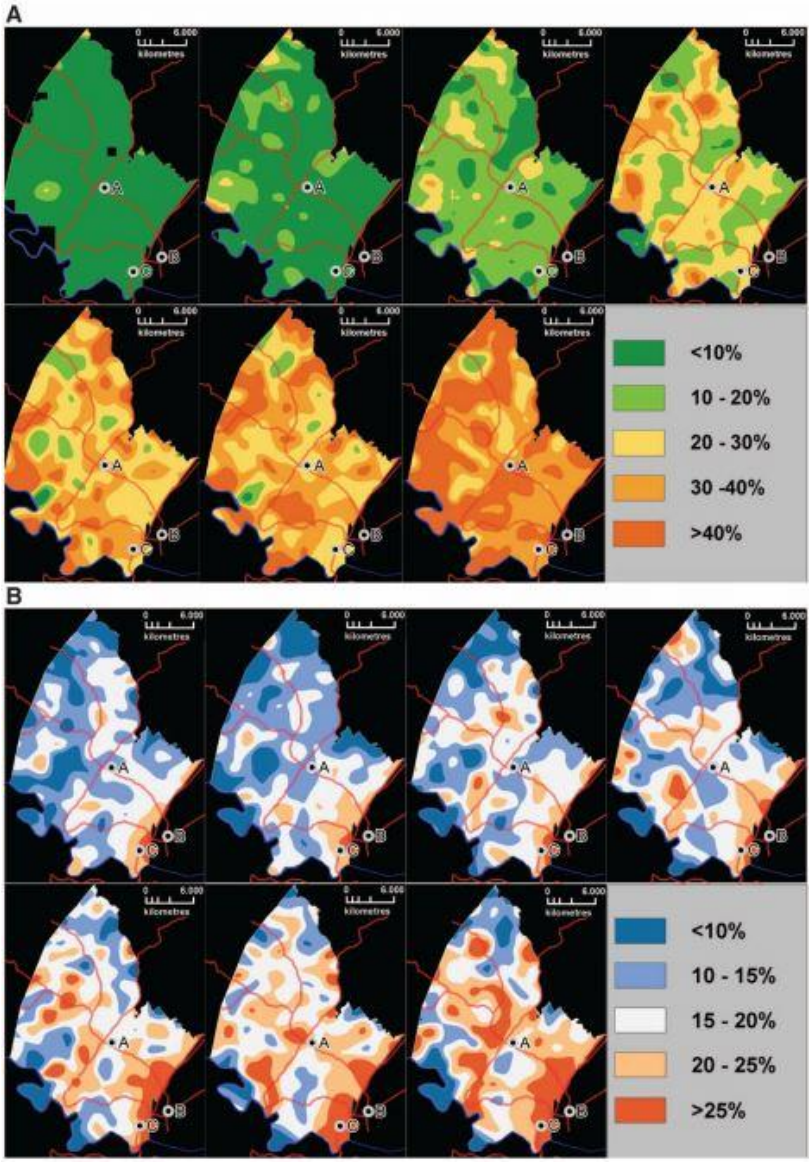

Fig. 1. Time series of maps showing the progression of the proportion of HIV-infected adults (>14 years of age) receiving HAART (A) and HIV Prevalence (B). Each map pixel correlates to the proportion of total HIV positive patients receiving HAART (A) and total HIV infected population (B) in the surrounding community as measure by a standard Gaussian kernel of 3 km radius

Table 1. HRQoL of ART-naïve and ART groups

	Total	ART-naïve	ART	P value
	N (%)	N (%)	N (%)	
Mobility				
No problems	844 (93.5)	397 (91.3)	444 (95.5)	
Problems	59 (6.5)	38 (8.7)	21 (4.5)	0.010
Self Care				
No problems	897 (99.3)	430 (98.9)	467 (99.8)	0.084
Problems	6 (0.7)	5 (1.2)	1 (0.2)	
Usual Activities				
No problems	885 (98.2)	423 (97.5)	462 (98.7)	0.167
Problems	17 (1.9)	11 (2.5)	6 (1.3)	
Pain/Discomfort				
No problems	680 (75.3)	316 (72.6)	364 (77.8)	0.074
Problems	223 (24.7)	119 (27.3)	104 (22.2)	
Depression/Anxiety				
No problems	782 (86.6)	372 (85.5)	410 (87.6)	0.357
Problems	121 (13.4)	63 (14.5)	58 (12.4)	
VAS score, median (IQR)	80 (70–95)	80 (70–90)	90 (80–100)	<0.0001

Table 2. The medical outcome study 36-item short form health scores at HAART initiation and the 12 month follow up visit. The IeDEA West Africa Collaboration, 2010-2011

	HAART initiation $n = 344$ Mean (SD)	12-month visit $n = 265$ Mean (SD)	Score change $n = 265$ Difference* (CI 95%)	p^*
	MOS SF-36 dimensions			
Physical functioning				
Women	73.5 (27.2)	98.9 (5.9)	+23.7 (26.6)	$<10^{-4}$
Men	75.4 (25.7)	99.0 (4.8)	+22.7 (26.0)	$<10^{-4}$
Physical-related role limitations				
Women	53.5 (45.7)	99.1 (5.9)	+43.8 (45.5)	$<10^{-4}$
Men	51.9 (45.5)	98.6 (9.5)	+44.9 (47.9)	$<10^{-4}$
Bodily pain				
Women	62.7 (28.9)	97.0 (10.0)	+32.6 (29.2)	$<10^{-4}$
Men	59.1 (26.5)	96.2 (11.3)	+36.3 (25.3)	$<10^{-4}$
General health perception				
Women	60.6 (25.6)	86.0 (12.3)	+24.4 (28.8)	$<10^{-4}$
Men	59.9 (27.4)	88.1 (8.9)	+26.2 (26.9)	$<10^{-4}$
Vitality				
Women	47.6 (17.6)	48.5 (9.4)	+0.5 (19.6)	0.74
Men	47.6 (16.8)	48.0 (8.6)	−0.4 (18.0)	0.87
Social functioning				
Women	71.1 (25.9)	96.4 (8.9)	+23.1 (25.4)	$<10^{-4}$
Men	70.8 (26.4)	96.2 (9.9)	+23.4 (25.3)	$<10^{-4}$
Emotional-related role limitations				
Women	62.7 (43.6)	99.5 (5.3)	+35.7 (43.7)	$<10^{-4}$
Men	62.6 (44.7)	98.6 (12.0)	+33.3 (45.4)	$<10^{-4}$
General mental health				
Women	55.6 (15.5)	54.5 (9.7)	−0.8 (18.4)	0.57
Men	57.9 (12.8)	54.5 (9.0)	−2.7 (15.2)	0.14
	MOS SF-36 composite scores			
Physical health summary score				
Women	45.6 (11.2)	60.0 (3.1)	+13.6 (11.4)	$<10^{-4}$
Men	44.9 (10.7)	60.1 (3.2)	+14.6 (11.0)	$<10^{-4}$
Mental health summary score				
Women	42.1 (8.9)	43.9 (3.4)	+1.8 (9.2)	$<10^{-2}$
Men	42.7 (8.0)	43.8 (3.3)	+0.8 (7.9)	0.41

*Matched paired t-test; *mean observed scores differences between 12-month visit and HAART initiation. SD = standard deviation; CI = confidence intervals; MOS SF-36 = Medical Outcome Study 36-Item short form; HAART = highly active antiretroviral therapy.

Overtime, 1413 seroconversions were observed, with the risk of infection to an individual being 34% less in an area where 30 to 40% of HIV positive individuals were on HAART (P <0.0001) compared to HAART coverage of less than 10% [7]. Holding confounding factors equal a steep and highly significant decline was observed in adjusted HIV acquisition hazard with increasing

HAART coverage [7]. This increased the original 34% decrease of likelihood to 38% on average ($P < .0001$) [7]. An adjusted hazard ratio of 0.986 was calculated such that a 1% increase in HAART coverage is correlated with a 1.4% decline in the risk of acquisition of a new HIV infection [7].

3.5 Stigma and Adherence

In a study conducted in Burkina Faso, with 306 patients on HAART and 106 patients not yet on HAART, attitudes and perceptions towards HAART were assessed [14]. Although many were unable to read and write, their general attitudes were positive towards HAART with 98% believing that AIDS could be controlled and daily function could be preserved with HAART [14]. However, the psychological burden of AIDS was apparent with 27% of participants concerned about others finding out that they were on HAART [14]. Although they were concerned about transmission, this perceptual stigma continued with only 22% of patients reporting their status to their partner [14].

In a similar qualitative study conducted by Bezahbe, W et al, in Ethiopia, patients cited that disclosure of HIV status to friends and family members was a facilitator of adherence [8]. Those who declared their status did not fear the stigma and discrimination to obtain and follow HAART regimens [8]. Status disclosure was also found to be an important factor that contributed to adherence via social support mainly in the form of reminders to take medication in a timely fashion [8]. Clinical staff had also noticed that food and transportation support also helped with adherence [8].

Stigma and discrimination was still reported by both patients and providers as a hindrance to adherence [8]. The avoidance of patients taking drugs in front of others kept them from maintaining and keeping their medications [8]. This led many to prefer to be treated in clinics far away from their homes [8]. Furthermore, the majority of patients were low wage laborers who did not have any privacy at their place of employment [8]. This negative stigma caused them to hide their pills from their employers and colleagues, fearing that they would lose their jobs if they were discovered [8]. This resulted in many subjects reporting that they did not take their pills on time [8].

Table 3. HIV mother-to-child transmission risk in the 1999-2008 and 2009-2011 periods, by prenatal antiretroviral, delivery route, and infant feeding prevention strategies, Dominican Republic

All perinatally exposed	142/1,274 (11.1%)	12/302 (4.0%)*
Any maternal antiretrovirals	54/861 (6.3)	10/267 (3.7)
HAART[1] all	4/157 (2.5)	5/174 (2.9)
AZT + 3TC + NVP[2]	4/157 (2.5)	0/59
AZT + 3TC + Lopinavir/r[3]	—	5/115 (4.3)
Non-HAART multidose AZT-containing regimen	4/80 (5.0)	—
Single-dose NVP ALL	32/506 (6.3)	3/60 (5.0)
8 hours precaesarean	25/395 (6.3)	0/2
Labor onset	5/78 (6.4)	—
At delivery	2/30 (6.7)	—
Unspecified	—	3/58 (5.2)
Unknown	14/211 (11.6)	2/30 (6.7)
None	88/413 (21.3)†	2/35 (5.7)*
Delivery		
Vaginal	68/285 (23.9)†	6/80 (7.5)*
Caesarean	60/882 (6.8)	5/199 (2.5)*
Unknown	14/107 (13.1)	1/23 (4.3)*
Infant antiretrovirals		
Single-dose Nevirapine (SD NVP)	48/782 (6.1)	1/41 (2.4)
SD-NVP after 72 hours	1/13 (7.6)	—
Zidovudine for six weeks	7/139 (5.0)	7/126 (5.6)
Unknown/other/none	32/340 (9.4)†	4/135 (3.0)
Infant feeding		
Breast fed only	25/67 (37.3)	0/2
Mixed	16/43 (37.2)	0/4
Formula only	79/972 (8.1)†	11/271 (4.1)*
Unknown	22/192 (11.5)	1/25 (4.0)*

*$P < .05$, comparison by time period, 1999–2008 versus 2009–2011.
†$P < .01$ within period, by strategy.
[1]Highly active antiretroviral therapy.
[2]AZT-3TC-NVP: zidovudine, lamivudine, nevirapine.
[3]AZT-3TC-Lop/r: zidovudine, lamivudine, lopinavir (ritonavir boosted).

Table 4. Comparison of HAART adherence between groups at 1st and 2nd assessments

		1st Assessment (before the program)			
		Adherent	Non-adherent	Total	*p*-Value[a]
2nd Assessment (after the program)	Adherent	48 (90.6%)	32 (65.3%)	80 (78.4%)	0.002
	Non-adherent	5 (9.4%)	17 (34%)	22 (21.6%)	
	Total	53 (100%)	49 (100%)	102 (100%)	

In a study done in Portugal by Ribeiro, C et al, a significant association was found between adherence to HAART regimens before and after a psycho-educational program was implemented (P = .002) (Table 4) [15]. Adherence was measured using CD4 counts of subjects [15]. Ninety-one percent of original adhering individuals adhered with their therapy till the end [15]. After the implementation of the program 65% of non-adherents to HAART became adherents [15]. This bought the total up in all samples for adherence from 52 to 78% [15]. With a similar implementation of a psychoeducative program in Morocco, patients with undetectable viral load went from 52% at baseline 72% at month 6 (*P* = .05) [9].

4. DISCUSSION

Through the expansion of HAART since its implementation, programs in low to middle income areas face the challenge of adapting to the growing numbers of patients seeking care [1]. However as HAART has become more widely accepted, a gradual improvement in disease severity at HAART initiation is noted with a subsequent decline in mortality following [1]. As programs expanded a mortality decrease in South Africa for 6 month survival estimates was observed to decline to less than 4% in 2011 from the 14% observed in 2004 [1].

Even with increased availability of HAART programs, long term follow up (LTFU) loss and adherence still remain major problems [10]. The mortality rate after LTFU was much higher especially during early HAART and in the time period 3 months immediately preceding the LTFU [10]. The mortality risk was three times higher for those patient LTFU than those that remained in HAART programs [10]. This LTFU may be attributed to many factors such as social stigmas and perception and related social support programs [8]. In the South Africa cohort, a novel finding was that as the program scaled up LTFU loss increased proportionally [1]. This leads to a need for timely adjustments in programs to handle the flood of new patients that inevitably come while still maintaining the same level of access to prior patients [1]. One proposed method to help increase adherence is to put in checks to make sure the qualities of the programs remain constant while dealing with a quantity surge [1]. Improved procedures are needed to ensure continuity and quality of care for LTFU patients to decrease mortality measures amongst this cohort [10].

Gender differences for mortality rates were also significant. Within patients starting HAART in South Africa from 2004 to 2009, men had a higher mortality than women [11]. The rise in mortality for men persisted across different analysis including adjustment for HIV severity at HAART initiation, patients who achieved viral suppression with HAART, and even in patients with a good immune response to treatment [11]. Late presentation of disease is cited as one of the reasons that may attribute to a higher male mortality, with men in Sub-Saharan Africa often starting treatment at a later age and with a more advanced clinical disease than women [11]. Although this disparity is frequently attributed to gender differences in health seeking behavior and healthcare referral, numerous systematic reviews have suggested gender inequalities to HAART access [11]. This emphasis on maternal and child care health services may lead to men's primary health care needs being neglected elucidating their delayed initiation of treatment [11].

HAART treatment was also found to increase Health Related Quality of Life (HRQoL). Comparisons of groups that were HAART naïve with groups on HAART yielded improved self-rated health scores (ED-5Q) [3]. Even when patients were grouped according to their baseline CD4 counts those on HAART reported better ED-5Q results [3]. This suggests that drug toxicities of patients on HAART had little correlation with their self-reported health [3]. In HAART naïve patients, those with CD4 counts >350, self-reported health scores were substantially lower [3]. Because of the large sample size of this

study, the strength between HRQoL and CD4 count can be realized [3].

In General HRQoL and physical, emotional and social well-being were also found to be improved on HAART consistently amongst studies assessing positive treatment outcomes [5]. Meaningful long term HRQoL improvements were noticed in one third of patients with no adverse impacts of therapy reported on HRQoL [5]. However, the fear and stigma of disclosure about treatment can negatively influence social relationships and general well-being [5]. Thus, treatment support groups, counseling and advice offered in studies can also account for some part in improvements in social relations [5]. This can lead to a shifting of attitudes about HIV from a death sentence to a disease that can be treatable with HAART [5]. This decrease in stigma then leads to a general increase in quality of social relations [5].

After a year of HAART, all physical components of HRQoL demonstrated improvement while the mental components did not keep the same pace of improvement [4]. Drug toxicities did not have an impact on physical and mental health scores (PMHS) but only toxicities severe enough to prompt a drug change were measured [4].This could have led to an underestimation of its true impact of drug toxicities in restoring patient's well-being [4]. Nevertheless, the number of symptoms subjects reported at each follow up visit correlated strongly with a decrease in PMHS [4]. Also, the higher the disease severity when starting HAART, the higher the increase in HRQoL [4]. Both of these facts are consistent with studies done in developed countries that correlate symptoms, HRQoL, baseline disease severity and therapy improvement [4]. The type of facility delivering treatment is also associated with stronger increases in HRQoL with a preference for centers run by NGO's versus public hospitals [4]. This may be due to the fact that until 2010 unlike NGO's public hospitals charged an access fee for HAART in Burkina Faso [4]. This demonstrates that availability and burden of cost could be a factor in perceived improvement. Thus, perceived barriers to access and symptom resolution must be promptly addressed to gain maximum HRQoL benefit from treatment [4].

Adherence to HAART during pregnancy, labor and breastfeeding by HIV positive mothers can lead to a vertical transmission rate of less than 2%, virtually eliminating spread even in countries where breastfeeding and vaginal delivery are the norm [6]. Monitoring maternal response to antiretroviral drugs by using viral load and drug sensitivity assays should be made universally accessible to confirm suppression of maternal viral load and ultimately successfully prevent transmission [6]. Due to a window period where mothers may test negative for HIV, a follow up test should be scheduled for all mothers who initially test negative [6]. Maternal HAART through prenatal and postnatal breastfeeding has proven to have less stigma and become more acceptable in underdeveloped countries [6]. This may have been due to the fact that the women were enrolled in antenatal care in a tertiary institution leading them to be of a wealthier class and more educated leading to better understanding and adherence of treatment and viral transmission [6]. Also, data collected on breastfeeding was based on patients recall so recall bias cannot be ruled out [6].

RT-PCR was found to be a useful tool in testing for HIV status [12]. When compared to prophylactic regimens, HAART proved itself to be superior in preventing transmission [12]. RT-PCR is an effective tool to confirm such results, leading to better clinical management [12]. It also allows for quicker diagnosis of HIV in children leading to quicker supervision [12]. However, in many impoverished areas financial constrains limit the availability of RT-PCR [12].

The revision of guidelines to make HAART more inclusive to HIV positive pregnant patients in the Dominican Republic advocates that MTCT elimination is attainable [13]. This change has coincided with an increase in the amount of pregnant patients receiving HAART and the consequential drop in MTCT rates [13]. The documented increase in patients on HAART also parallels an increase in bottle feeding for infants and a national drop in the prevalence of HIV and unsafe sexual practices [13].

The weak link in these positive findings is the advising of women of their HIV status and connecting them with the proper care and HAART [13]. The guidelines for testing includes two rapid positive tests to confirm HIV status which in theory is supposed to let women know at least their presumptive status the same day [13]. However through observational studies and case reports, samples for the second test are often stored to be tested at one time together and women who are have a presumptive positive without a confirmatory test are asked to return

without being informed of the positive screening test [13]. Many women not return and end up delivering without ever knowing their status and receiving any HAART [13].

Another hindrance is the requirement in certain areas for women to go to specialized clinics to receive HAART [13]. Often they will continue with prenatal care but never visit the specialized clinic to receive treatment [13]. This absence of treatment leads to a very high risk for vertical transmission compared to those mothers who are treated with HAART [13]. Social stigma is also very strong to avoid testing as in the past women who didn't receive their results found that they had been given to their employers or family members [8,13]. This fear of discrimination coupled with a law that makes it a crime for an infected person to have even protected intercourse with an uninfected person will deter women who suspect their status from receiving treatment and thus putting their children at risk [13]. Survival bias was also high in determining the number of infants infected since up to 30% of infected infants don't survive past two years in the Dominican Republic [13].

The expansion of HAART also has a significant effect for those who are unaffected in a region by decreasing their chances of contracting the infection [7]. A key predictor for horizontal transmission of HIV was prevalence of infection in the community surrounding an uninfected individual [7]. An individual was 2.2 times more like to become infected in a community where more than 25% of the people were infected compared to the baseline community of less than 10% infected [7]. Moreover to exclude the influence of the scale up of other HIV prevention programs which could have correlated with HAART, time trends in six variables were analyzed [7]. The only variable that increased significantly was condom usage from 2005 to 2011 [7]. Even controlling for this, the strong relationship between HAART and the risk of acquiring HIV remained unaffected [7]. This null finding can be attributed to condoms only being an effective long term preventative tool when used correctly and consistently [7]. Community changes over time were also ruled out as having an effect on the HAART findings by adding time period dummy variable to the regression equation [7]. The HAART coverage outcome was able to sustain various sensitivity variables to account for different prevention activities and time analysis trends [7]. As age increased so did ART coverage and subsequently the risk for contraction also decreased consistent with the "prevention as treatment" hypothesis [7]. The results continued to hold when using an alternate Isigodi Zulu area fixed effects analysis [7]. The results from this study helped to consolidate the HPTN 052 study which revealed that viral transmission could be decreased by 96% with strict HAART adherence amongst sexual partners [7]. This analysis is in agreement with mathematical models that predict the decrease in HIV horizontal transmission with the expansion of HAART further encouraging the urgency to scale up treatment for not only patients but for the effects it has on the unaffected population [7].

The full effectiveness of HAART for affected and unaffected patients cannot be achieved until the negative perception and stigma associated with it are fully obliterated. In a study undertaken in Burkina Faso, we can observe that attitudes are changing [14]. An overwhelming majority of patients not only demonstrated positive attitudes towards HAART but 95% indicated they had not missed their medication within the previous week and 94% had not missed it for more than 3 days ever [14]. This high level of adherence indicates the value patients are realizing in HAART [14]. Several similar sub-Saharan studies have demonstrated that it is possible to achieve a 95% adherence rate in up to 80% of patients [14]. It must be noted that self-reported adherence does not always correlate with plasma concentrations of medication or viral load [14]. In future studies a recommendation of using more than one method to measure adherence is desirable [14].

In the Amhara region of Ethopia, although economic constraints were recognized as the greatest barrier to adherence, another important factor was the discrimination that a person with HIV/AIDS has undesirable qualities making him less worthy in the eyes of society [8]. This combination of stigma experience by the patients, the lack of adequate privacy to take their treatment and discrimination hindered adherence greatly [8].

Sexual intercourse, the most important route of transmission of HIV, is also overwhelming negatively influenced by perceived stigma [14]. Although patients would benefit from proper condom usage, only 22% reported their HIV status to their partners [14]. The study found that a patient's tendency to disclose could not be correlated with infection duration, sex, or social support [14]. This may indicate that although there are large media campaigns and community

sensitization programs in Burkina Faso to target stigmatization, it still remains a major concern for those living with HIV [14]. A similar troublesome fact was that only 42% of the participants reported condom usage during sexual intercourse [14]. Condom usage was less likely in married or cohabiting couples, supporting consistent reports that in Africa condoms are often reserved for having sex with someone other than a spouse [14]. This indicated that although HAART is generally well accepted with good reported adherence, patients face concerns about stigmatization that manifest when it comes to the most common form of transmission. Much work must still be undertaken to combat this stigmatization to decrease transmission if one day we hope to eradicate HIV. One possible avenue for achieving this is patient education with behavioral modification.

In a study undertaken Portugal, the implementation of a psycho-educational program with both behavioral and educational approach proved successful in promoting HAART adherence, measured significant gains in the CD4 T lymphocyte levels in patients [8]. This immune status based assessment also showed a significant reduction in HIV-RNA averages [8]. This immune status based method of measuring adherence helped to eliminate the overestimation that may be present be self-reporting [8]. The educational part of the program proved effective when the average knowledge of the HIV virus increased in the administered questionnaires before and after the program [8]. By remaining adherent, patients delay or avoid the resistance to HAART leading to more treatment options and delayed disease progression [8]. Through this lens, the educational program proves it relevance as part of a comprehensive strategy by improving adherence [8]. While realizing the many gains of HAART, such multi-faceted approaches work to battle negative stigma and perception, ultimately showing to increase adherence and result in better outcomes for patients and communities in which they reside.

5. CONCLUSION

As HAART expands, several issues have to be addressed concerning patient attrition and access for mortality rates to continue to decrease [1]. This is implied by higher rates of mortality amongst patients lost to LTFU [10]. One area that can be agreed has higher mortality implications is males [11]. Whether it is healthcare access issues or societal stigmas, males often present later with a higher disease severity and are less likely to be adherent to treatment [11]. A successful program strategy must be developed in which patients inclined to be LTFU have their issues addressed and long term retention rates are given priority along with extensive program roll out [10].

The initiation of HAART correlated with an improved HRQoL [5]. Patients reported better scores amongst a variety of subsections on HAART versus patients who were not on therapy [5]. Improvements were evident in both physical and mental dimensions of patients HRQoL [4]. This was especially evident in patients with low immunological status who showed precipitous improvements in HRQoL [4].

HAART also demonstrated considerable decrease in vertical transmission risk compared to standard prophylactic protocols [12,13,6]. These risks were well documented in the Dominican Republic when policy changes increased the amount of HIV positive pregnant women receiving HAART and a subsequent vertical transmission decline was observed in the following years [13].

The efficacy of wide spread coverage of HAART and its effect on horizontal transmission was documented using data and mathematical and statistical regression models [7]. In comparison to areas where less than 10% of patients were on HAART the results demonstrated that as the level of HAART coverage in a community increased, the risk of contracting HIV decreased inversely [7]. It also showed that the risk of acquiring HIV increased as its prevalence increased [7].

Although HAART has been very effective in reducing mortality and transmission risks and improving HRQoL, one of its vulnerable points has been adherence. Although studies show that HAART is very well accepted in many communities, there is still a large stigma associated with HIV/AIDS [14]. This stigma causes fear which often leads to unsafe sexual practices thereby transmission risk [14]. Another factor is the absence of privacy combined with fear of retribution from social and employment circles causing missed treatment doses that subsequently leads to an increase in viral load [8,13]. One effective method shown to combat stigma and improve patient outcomes is psychoeducational programs that combat bad behavior while educating patients [8]. One

interpretation of these programs is that via education patients are empowered to make better decisions and subsequently increase their own HRQoL while decreasing transmission to others via risky behaviors [8].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Grimsrud A, Balkan S, Casas EC, Lujan J, Van Cutsem G, Poulet E, et al. Outcomes of antiretroviral therapy over a 10-year period of expansion: A multicohort analysis of African and Asian HIV programs. J Acquir Immune DeficSyndr. 2014;67(2): e55-66.
2. Cunningham WE, Wong M, Hays RD. Case management and health-related quality of life outcomes in a national sample of persons with HIV/AIDS. J Natl Med Assoc. 2008;100(7):840-847.
3. Nglazi MD, West SJ, Dave JA, Levitt NS, Lambert EV. Quality of life in individuals living with HIV/AIDS attending a public sector antiretroviral service in Cape Town, South Africa. BMC Public Health. 2014;14: 676.
4. Jaquet A, Garanet F, Balestre E, Ekouevi DK, Azani JC, Bognounou R, et al. Antiretroviral treatment and quality of life in Africans living with HIV: 12-month follow-up in Burkina Faso. J Int AIDS Soc. 2013;16:18867.
5. Tomita A, Garrett N, Werner L, Burns JK, Ngcobo N, Zuma N, et al. Impact of antiretroviral therapy on health-related quality of life among South African women in the CAPRISA 002 acute infection study. AIDS Behav. 2014;18(9):1801-1807.
6. Okafor I, Ugwu E, Obi S, Odugu B. Virtual Elimination of mother-to-child transmission of human immunodeficiency virus in mothers on highly active antiretroviral therapy in Enugu, South-Eastern Nigeria. Ann Med Health Sci Res. 2014; 4(4):615-8.
7. Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science. 2013;339(6122):966-971.
8. Bezabhe WM, Chalmers L, Bereznicki LR, Peterson GM, Bimirew MA, Kassie DM. Barriers and facilitators of adherence to antiretroviral drug therapy and retention in care among adult HIV-positive patients: A qualitative study from Ethiopia. PLoS One. 2014;9(5):e97353.
9. Khachani I, Harmouche H, Ammouri W, Rhoufrani F, Zerouali L, Abouqal R, et al. Impact of a psychoeducative intervention on adherence to HAART among low-literacy patients in a resource-limited setting: The case of an Arab country--Morocco. J IntAssoc Physicians AIDS Care (Chic). 2012;11(1):47-56.
10. Cornell M, Lessells R, Fox MP, Garone DB, Giddy J, Fenner L, et al. IeDEA-Southern Africa Collaboration. Mortality among adults transferred and lost to follow-up from antiretroviral therapy programmes in South Africa: A multicenter cohort study. J Acquir Immune Defic Syndr. 2014;67(2):e67-75.
11. Cornell M, Schomaker M, Garone DB, Giddy J, Hoffmann CJ, Lessells R, Maskew M, Prozesky H, Wood R, Johnson LF, Egger M, Boulle A, Myer L. International epidemiologic databases to evaluate AIDS southern Africa Collaboration. Gender differences in survival among adult patients starting antiretroviral therapy in South Africa: A multicentre cohort study. PLoS Med. 2012;9(9):e1001304.
12. Linguissi LS, Bisseye C, Sagna T, Nagalo BM, Ouermi D, Djigma FW, et al. Efficiency of HAART in the prevention of mother to children HIV-1 transmission at Saint Camille medical centre in Burkina Faso, West Africa. Asian Pac J Trop Med. 2012;5(12):991-994.
13. Lorenzo O, Beck-Sagué CM, Bautista-Soriano C, Halpern M, Roman-Poueriet J, Henderson N, et al. Progress towards elimination of HIV mother-to-child transmission in the Dominican Republic from 1999 to 2011. Infect Dis Obstet Gynecol. 2012;543916.

14. Guiro AK, Traore A, Somda A, Huang SL. Attitudes and practices towards HAART among people living with HIV/AIDS in a resource-limited setting in northern Burkina Faso. Public Health. 2011;125(11):784-790.

15. Ribeiro C, Sarmento E Castro R, Dinis-Ribeiro M, Fernandes L. Effectiveness of psycho-educational intervention in HIV patients' treatment. Front Psychiatry. 2015; 5:198.

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