Chapter 7. Treatment

Antiretroviral therapy has transformed HIV to a chronic - though still incurable - virus requiring ongoing therapy and strict adherence to treatment. For the most part, virally suppressed people living with HIV today have no difference in life expectancy than demographically similar HIV-negative individuals (Sabin, 2013 cited in Justice and Falutz, 2014; Maman et al. 2012a).

While no documented cases of a true cure exist (Dieffenbach and Fauci, 2011), “investigators and scientists seek to completely eradicate HIV infections (called by some a sterilizing cure) or allow patients to interrupt antiretroviral therapy (ART) without the risk of viral rebound (known as a functional cure)” (Margolis, 2014: 1069). Unfortunately, an HIV cure that is broadly applicable has yet to be found (Colasanti et al., 2014). While progress has been achieved, “the global response will clearly have to be sustained for at least several decades” (Piot and Quinn, 2013: 2216).

Treatment Programming Must Continue to be Scaled Up
Access to ART has been steadily increasing. By the end of 2013, more than 11.7 million people were on ART in low and middle-income countries, representing about one-third of those living with HIV (Stover et al., 2014). However, 22 million people who need it are still not accessing ART (UNAIDS, 2014a). Reductions in HIV funding threaten to interrupt treatment provision. Interrupted or episodic treatment increases individuals’ risk for drug resistance, disease progression and death (SMART Study Group, 2006; Kaufmann et al., 2011).

The benefits of ART are widely known to increase life expectancy, quality of life and the ability to work and perform daily activities for people living with HIV (Antiretroviral Therapy Cohort Collaboration, 2008). Accelerating treatment access for adults with young children can reduce the numbers of orphans, and improve pediatric survival and social wellbeing. [See also Care and Support: Orphans and Vulnerable Children] Furthermore, many studies have shown that providing ART is cost-effective (Bor et al., 2012; Koenig et al., 2011; Walensky et al., 2011; Iwuji et al., 2011). Conversely, “failure to scale up ART…would mean a sizable reduction in national economic activity, many fewer healthcare workers and teachers and worse educational outcomes for today’s generation of children, in addition to the humanitarian impact of increased mortality” (Holmes et al., 2010a: 177). A recent analysis by the Global Fund found that economic returns on AIDS treatment, through improved worker productivity

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This section does not provide clinical guidance, which is available from WHO, but rather a public health perspective on what works for women to access treatment, adhere to antiretroviral therapy and to reduce transmission and stay healthy.

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and by averting future costs to care for children orphaned by the epidemic may equal or outweigh the costs of treatment (GFTAM, 2010 cited in AIDS2031 Consortium, 2010).

WHO’s 2013 ART guidelines were designed to increase the potential number of people eligible for ART to 28.6 million by calling for treatment initiation when a patient’s CD4 count falls below 500 cells/µl rather than the earlier standard of 350 (WHO, 2014a). WHO modeling shows that the incremental cost of moving ART initiation criterion from CD4 counts of under 350 to under 500 is “relatively small,” (WHO, 2013: 97) but people needing treatment could increase by 25% (WHO, 2013: 97). Scaling up access to ARVs as per WHO 2013 guidelines would cost US$350 per quality life year gained, “well below the cost-effectiveness threshold recommended by the Commission on Macroeconomics and Health” (Stover et al., 2014: S228).

Several modeling studies have been carried out estimating the cost-effectiveness of expanding ART initiation and found that doing so could result in highly cost-effective interventions with improved survival rates and reduced transmission. A study in South Africa found with estimates at 5 and 40 years (for the year 2050), expanding ART initiation guidelines to those with CD4 counts less than 350 cells/µl, those with counts of less than 500 cells/µl and all CD4 levels result in cost savings in the long run as compared to the current regimen (at the time of the study) of ART initiation at 200 cells/µl. With each increasing level of CD4 initiation, there is a corresponding decrease in mortality and in transmission rates (Granich et al., 2012).

Mathematical models used to evaluate the health outcomes, cost, and cost-effectiveness of different adult ART eligibility criteria in South Africa, Zambia, India, and Vietnam found that expanding treatment coverage to adults with CD4 counts at or below 500 cells/µl in a generalized epidemic was cost-effective and that expanding treatment to key affected populations with CD4 counts at or below 500 cells/µl in concentrated epidemics was cost-effective (Eaton et al., 2014; Eaton et al., 2013). A modeling study in Mozambique demonstrated that point-of-care CD4 testing could improve treatment outcomes through nearly one year of additional life expectancy, and be cost-effective compared to lab-based CD4 testing, provided linkages to care were improved (Hyle et al., 2014).

Yet, some question how much effort should focus on increasing access to treatment for people whose CD4 counts are over 350 when access to treatment for individuals under 350 is still not universal (Anglemyer et al., 2013). In fact, a review of 379,865 patients from seventeen low- and middle-income countries found that median CD4 counts increased in lower income countries between 2000 and 2009 but still remained under 200 (Avila et al., 2014). If guidelines reduce the opportunities for people with low CD4 counts to initiate treatment, this could increase inequities and mortality at a population level (Cohen et al., 2013). Experts have argued that finding, treating and retaining people with high viral loads or low CD4 counts should be the priority rather than treating healthy people (Bassett and Brudney, 2013). Given the results of the START study that showed that early initiation of ART (above CD4 counts of 500) had beneficial health effects, as well as the study results of HPTN 052 that showed that early treatment reduced HIV transmission, how to scale up universal access to testing and
treatment in a way that respects human rights, choice, and the ability of people living with HIV to decide when they are ready to adhere to treatment for life remains a global challenge.

**Women Have Particular Treatment Needs and Risks**

Women constitute a higher proportion of those receiving ART than men; likely due to greater interactions with the health care system for pregnancy and child-related care. For all low- and middle-income countries, women make up 51% of those eligible for care but make up 59% of those receiving ART (WHO et al., 2013). However, while more women than men have accessed treatment globally, structural factors and traditional gender norms can jeopardize women’s adherence, retention in care and their ability to prevent acquisition (if HIV-negative) or reduce transmission (if HIV-positive). [See Strengthening the Enabling Environment]

While many treatment strategies have been evaluated as a whole, very little sex-disaggregated data or analyses have been published in 30 years of the epidemic to evaluate what works in treatment for women, especially when separating out data for pregnant women.

Other issues such as cardiovascular disease, osteoporosis and drug resistance have important implications for women living with HIV. For example, HIV, even for those on ART and virally suppressed, is an independent risk factor for cardiovascular disease (Freiberg et al., 2013; Islam et al., 2012 cited in So-Arma and Freiberg, 2014) and young African women living with HIV seem to be at particular risk. In an analysis of a group of 741 women under age 35 with advanced HIV disease from seven countries in Sub-Saharan Africa, nearly all women had no signs of cardiovascular disease when they initiated ART. However, after 144 weeks of follow up after ART initiation, increases in all cardiovascular risk factors were seen (Shaffer et al., 2014). A cross-sectional study in Malawi showed that cardiovascular risk factors – including insufficient fruit and vegetable diet, high blood pressure, weight gain, increased cholesterol levels, and low physical activity – were all common among long-term ART patients (Muronya et al., 2011). Some studies have shown that women are also at higher risk of osteoporosis, which is more common among those living with HIV (Mallon, 2014). Even though women have higher CD4 cell counts than men following HIV seroconversion, when men and women have the same level of viral loads, progression to AIDS is faster in women (Addo and Altfeld, 2014). Little is known about long-term outcomes among people living with HIV in lower- and middle-income countries with regard to how ART affects cardiovascular and pulmonary diseases (Bloomfield et al., 2014).

Following ART initiation, some studies have found different side effects for women than for men suggesting the need for “sex specific approaches to ART” (Addo and Altfeld, 2014: S91). Though the 2013 WHO guidelines do not include monitoring recommendations for disaggregation of data by sex, only distinguishing between pregnant and breastfeeding women and other adults (WHO, 2013), UNAIDS now recommends core indicators that include disaggregation by sex and age for percentage of adults currently receiving ART and percentage of adults with HIV known to be on treatment 12 months after initiation of ART (UNAIDS, 2014a). The Global Fund to Fight AIDS, Tuberculosis and Malaria also now
requires sex- and age-disaggregated data. Such disaggregation can illuminate potential discrepancies in ART outcomes for women and men.

Drug resistance is a risk for everyone. However, in a review of outcomes comparing nevirapine and efavirenz among 114,391 patients, nevirapine-based ARVs were significantly more likely to lead to resistance and virologic failure. Yet, overall, more women have been placed on nevirapine, as until recently efavirenz was contraindicated during pregnancy. “This analysis found that the [treatment] benefit of efavirenz over nevirapine was especially highlighted in resource-limited settings when compared to resource-rich settings” (Pillay et al., 2013: para 34). Single dose nevirapine was used for many years as the mainstay of antiretroviral therapy for pregnant women to reduce vertical transmission without assessing the impact of single dose nevirapine on the mother’s future treatment options. [See Safe Motherhood and Prevention of Vertical Transmission: Antenatal Care – Treatment]

Women may be at greater risk for becoming drug resistant themselves or transmitting drug resistant strains due to the temporary use of antiretrovirals to reduce perinatal transmission. Further evaluation is needed to understand these risks. While it is clear that those who go on ARV therapy for their own treatment needs should not interrupt treatment (Fauci, 2009a; SMART Study Group, 2006), treatment interruption for women who are on HAART simply to prevent perinatal transmission rather than for their own health needs is currently being evaluated under the PROMISE study. “The risk for maternal health of stopping…maternal triple ARV prophylaxis after breastfeeding cessation is unknown” (WHO, 2010i: 47) – especially if a woman living with HIV has multiple pregnancies. WHO recommendations for Option B+, i.e., lifelong treatment for pregnant women, may reduce stopping and re-starting ART which can carry increased risk for women’s mortality and morbidity. [See Safe Motherhood and Prevention of Vertical Transmission: Antenatal Care – Treatment] Women living with HIV globally have had mixed opinions around Option B+, and have raised concerned about possible human rights violations and the lack of choice in when to start treatment (for their own health), lack of community-based support, and health system challenges that need to be addressed for Option B+ to work effectively (Hsieh et al., 2014).

Successful and promising strategies for treatment can be further broken down into the following sections: provision and access; adherence and support; and staying healthy and reducing transmission. Many of these strategies can be applied to both men and women in gender-responsive ways.

A. Provision and Access
B. Adherence and Support
C. Staying Healthy and Reducing Transmission

“...We are more than mothers...”
(Dilmitis, 2014: 5)
What Works in Treatment

Treatment: Provision and Access

Antiretroviral therapy has been successfully administered in a range of situations with adherence, retention, and clinical outcomes similar to those achieved in resource-rich countries. Increasing provision and access, grounded in human rights based approaches, across all populations is critical to continuing that success.

Treatment Must Be Equitably Available to All in Medical Need

At the end of 2013, there were 12.9 million people receiving ART globally and the percentage of people living with HIV who are not receiving ART has been reduced from 90% in 2006 to 63% in 2013 (UNAIDS, 2014a). However, further efforts are needed to ensure that treatment is equitably available to all who can benefit from ART. There are substantial treatment gaps within regions and among groups. In 2013, 37% of adults living with HIV worldwide received ART, but only 24% of children living with HIV did (UNAIDS, 2014b).

Treatment access is based on WHO’s 2013 guidelines which call for a seamless continuum of care between HIV testing and counseling, linkage to care, enrollment in care, retention in care, preparing for ART plus ART initiation, with retention and adherence, and monitoring response and toxicity (WHO, 2013: 56-57).

Increased Access Must Also Include Respect for Human Rights

Expanding access to ART along with considerations of equity and human rights is urgently needed (ITPC, 2014). A recent review of data from over 50 countries found that one in eight people living with HIV is denied health care (UNAIDS, 2015). WHO’s 2013 guidelines also note “human rights and ethical principles should guide…national treatment policies to ensure that they are equitable and meet the specific needs of all beneficiaries” (WHO, 2013: 202). Requiring people living with HIV to disclose their serostatus to sexual partners and/or community members in order to receive treatment, care or support is a human rights violation. Similarly, coercing women to accept contraception in order to access treatment violates women’s rights to make their own fertility choices. [See Meeting the Sexual and Reproductive Health Needs of Women Living With HIV]

While “treatment buddies” can be supportive, requiring a treatment buddy or medical companion to access ARV therapy may place undue burdens on women and their children: a study of 1,453 patients in Uganda (71% female) on the impact of requiring people to disclose their HIV status and have a “treatment buddy” or “medical companion” to access ARV therapy found that of the women, 41% chose a child as their medical companion versus 14% of the men. Women feared disclosing their serostatus to
their husbands: only 31% of married women chose their husband as their medical companion, compared with 66% of married men who chose their wife (Foster et al., 2010b). In addition, individuals with limited networks may delay enrolling in or may drop out of care when treatment support “buddies” are required (Lahuerta et al., 2013). [See also Adherence and Support] Furthermore, in settings where the epidemic is concentrated among marginalized and stigmatized populations, such as sex workers, people who inject drugs and MSM, treatment access is also low (Hirnschall et al., 2013: para 2). [See Prevention for Key Affected Populations] Treatment programming could benefit from a conceptual framework similar to that developed for family planning, to ensure that public health programs that aim to increase treatment access and adherence “respect, protect and fulfill human rights in the way they are designed, implemented and evaluated” (Hardee et al., 2013: v).

**Women and Men’s Access to Treatment Differs**

To date, more women than men have accessed treatment. The majority of women benefit from health system access through dedicated reproductive and child health clinics (Braitstein et al., 2008b) but it is unclear whether the majority of women accessing ART are doing so only as part of safe motherhood and prevention of vertical transmission. Global attention has often focused on prevention of vertical transmission (UNAIDS, 2011b), putting men simply in the role of supporting their HIV-positive female partners to access services, rather than caring for their own needs. Men tend to initiate treatment later, are more likely to be lost to follow up, and have higher mortality rates (Siu et al., 2012).

The Institute of Medicine notes that for PEPFAR data, each year around two-thirds of those who enroll in ART are women; the proportion has remained steady over time (IOM, 2013). Patient data from 307,110 adults from Kenya, Mozambique, Rwanda and Tanzania between 2006 and 2011 found that risk of late enrollment (CD4 counts under 350) was significantly higher for men and nonpregnant women as compared to pregnant women (Hoffman et al., 2014).

A global review based on 36 studies in resource-rich and resource-limited settings found that being a heterosexual male was a consistent risk factor for presenting with low CD4 counts, resulting in less favorable outcomes for men once enrolled in treatment (Mukolo et al., 2013). An analysis of 23 cohort studies from Africa, including 216,008 participants found that only 35% of those accessing ART were men, despite an HIV prevalence of 40%, representing “a significant underrepresentation of men in ART programs” (Druyts et al., 2013: 419). In addition, the risk of death for men was 1.37 higher than for women. However, men are seldom targeted for treatment as they are not often classified as vulnerable or marginalized (Kanters et al., 2013). While this inequitable access for men to ART may be due, in part, to a focus on maternal health, equitable access to ART for men “should be conducted without …threatening HIV…treatment for women” (Druyts et al., 2013: 424).
Gender Norms Affect Treatment Access for Women and Men

Gender norms affect treatment access. A study of gender differentials in uptake to ART in Zambia found that men were more likely to refuse ART even though men’s self-rated health was lower than women’s, with norms of masculinity presenting the biggest barrier for male uptake of ART (Gari et al., 2014). Focus group discussions with men in Uganda found that men found it difficult to seek treatment, which contradicted their assumed masculine autonomy and superiority (Siu et al., 2013). A study of programmatic data on 334,557 adults enrolling in HIV care at 132 facilities in Kenya, Mozambique, Rwanda and Tanzania found that men were more than 1.6 times more likely to initiate ART with advanced HIV disease (CD4 count under 100) compared with women and that “this disparity seems to be widening with time” (Lahuerta et al., 2014: 435). A recent study found that men used their economic and decision-making power to informally access ART in order not to be seen at clinics, which are seen as a woman’s space. Out of shame, men suffered silently and attempted to cope by stealing their wives’ ARVs. The practice of men stealing ARVs from their wives endangered both partners and jeopardized women’s adherence (Nyamhanga et al., 2013).

Gender norms may also be critical for the higher uptake of ARVs by women, as explained by one Vietnamese woman living with HIV: “Women have no choice but to take the drugs. Meanwhile, men are the ones who consider whether or not to take the drugs because they don’t need to think of anything else except themselves” (Nguyen et al., 2012: 343). Greater attention needs to be paid to ensuring that men living with HIV know their serostatus, have equitable access to treatment, are virally suppressed and have access to condoms.

HIV is seen as a threat not just to a man’s health, but to his masculinity, requiring him to seek care, challenging his notions of fearlessness, and fueling fears of humiliation and that his wife will desert him. (Nyamhanga et al., 2013)

Sex Differences May Also Play a Role in Clinical Outcomes and Must Be Further Explored

Access to treatment by sex has been disaggregated in a number of studies. However, few studies have analyzed sex differences. “Although data are limited, there is also evidence that women may metabolize and respond to specific medications, including ARV drugs, differently than men” (Gandhi et al., 2004, Floridia et al., 2008, Ofotokun et al., 2007 cited in DHHS, 2011: 104). Studies to date have not shown differences in virologic efficacy of ART by sex (Collazos et al., 2007; Fardet et al., 2006; Currier et al., 2010 cited in DHHS, 2011), although “this conclusion is drawn from a limited evidence base” (d’Arminio Monforte et al., 2013: 30). ARVs are administered at fixed dosages that do not take into account the different body weight, etc. of each sex (d’Arminio Monforte et al., 2013). A study in Tanzania – in which 70% of the 234 patients were women – found that after one year of standard ART, a higher proportion of females had an undetectable viral load but with a lower CD4 cell increase than men. Women started treatment at a less advanced disease stage but lost their immunological advantage over men despite a better virological treatment response. In addition, men were better informed about the use of ART (Mosha et al., 2013). Other studies have found that men are disadvantaged in ART due to differences in body weight compared to dose (Tayler-Smith et al., 2010 cited in IOM, 2013).
A number of studies have suggested that gender or sex may influence the frequency, presentation, and severity of selected ARV-related adverse events (Clark et al., 2005 cited in DHHS, 2011; Hawkins et al., 2011 cited in Johannessen, 2011). One study found differences in virologic failure by sex, with women having an advantage over men (Firnhaber et al., 2012b). Another study also found that women were more likely to have viral suppression and better ART outcomes (Kipp et al., 2010) and another study found that women were in better clinical condition than men (Nunes et al., 2010). In some studies, however, women experience more adverse drug reactions than men (Hasan et al., 2011).

The research community recognizes the need to better understand the potential role of sex differences in HIV disease progression and treatment response (Heidari et al., 2010), with women under-represented in clinical trials (d’Arminio Monteforte et al., 2010). A review of forty randomized controlled trials for 18 new drug applications for antiretroviral therapy submitted to the US Food & Drug Administration (FDA) between 2000 and 2008 found that only 20% of trial participants were women (Soon et al., 2012). Even when women are included, sex-specific analysis of the data is rarely undertaken (Anderson, 2012). No studies have addressed the possible interactions between ART and hormones in both men and women, including pre, peri or post-menopause (d’Arminio Monforte et al., 2013).

Pregnancy represents an additional sex-related factor in treatment. In a study of 4,531 women from numerous treatment sites in Sub-Saharan Africa, one-third experienced a pregnancy within four years of ART initiation (Myer et al., 2010). Yet few treatment programs are designed with the likelihood of pregnancy in mind (Myer et al., 2010). Most of the world’s women living with HIV are of reproductive age and will need either contraception, discussions on how best to safely become pregnant and/or have a safe motherhood and reduce the risk of vertical transmission. [See Meeting the Sexual and Reproductive Health Needs of Women Living with HIV and Safe Motherhood and Prevention of Vertical Transmission]

Inequitable Treatment Access Affects Both Young and Old
Some studies have found that equity in access differs by age group with inadequate treatment access for adolescent women. Key affected populations, such as sex workers and those who use drugs, may face many barriers in accessing treatment as well (Ford et al., 2013b).

In 2013, there were 4.2 million people living with HIV over age 50 (UNAIDS, 2014a), and every year, almost 120,000 people in this age group acquire HIV (Nakagawa et al., 2013; Mahy, 2014). Modeling estimates that the numbers of people living with HIV over age 50 will rise to 9.1 million in 2040 in Sub-Saharan Africa (Hontelez et al., 2012). Older people living with HIV are more likely to have other chronic noncommunicable diseases, such as diabetes, cancer, and hypertension (Rabkin et al., 2012; Newman et al., 2012). Combining ART with other medications needed to treat the co-morbidities that come with aging can be challenging, with guidelines needed for this growing population (Cardoso et al., 2013). For women, menopause may increase the risk of HIV transmission and acquisition due to the thinning of the vaginal wall, with increased lesions and tears (UNAIDS, 2013). Yet little research has
been conducted on the sexual behaviors of people over age 50 (UNAIDS, 2013) and most surveys, such as DHS, do not include data for those over age 50 (Bendavid et al., 2012b).

The Cost of Treatment and Service Delivery Varies Widely and Can Affect Access

Cost is another factor in treatment access. Treatment provided at no cost can substantially increase both women and men’s access to ART (Musoko et al., 2011). For women especially, who may have additional barriers in accessing resources for transportation fees, childcare and more, providing treatment at no cost may substantially increase women’s access.

Treatment costs vary widely between sites but per-patient costs drop rapidly as care is scaled up. Calculated costs include medication and other costs associated with providing treatment and follow-up. Across 43 PEPFAR-supported ART clinics in Botswana, Ethiopia, Nigeria, Uganda, and Vietnam, costs for providing treatment and care for a newly initiated adult on ARVs ranged from US$61 at one site to US$3,301 at another (Menzies et al., 2011). Even within the same country – Kenya – studies found a wide range of costs per patient per year, ranging from US$77 in one site to US$1,160 in another site (Harding et al., 2010).

The use of generic drugs can result in substantial cost savings. Annual surveys from 2005 to 2008 of ARVs purchased in 16 countries by PEPFAR implementing and procurement partners found that availability of generic ARVs was associated with increased ARV procurement and cost savings of more than US$323 million over the four year period, with generics accounting for almost 90% of the 22 million ARV packs purchased with PEPFAR funds in 2008 (Holmes et al., 2010b). South Africa’s scale up of treatment resulted in a 53% reduction in the cost of ART, with projected two-year savings of $640 million (UNAIDS Treatment, 2015 cited in Dilmitis, 2014).

The Optimal Timing of Initiating ART Is As Soon As Someone Is Diagnosed with HIV and Chooses to Start Treatment

In May, 2015 the U.S. National Institutes for Health (NIH) announced that the Strategic Timing of Antiretroviral Treatment (START) trial was releasing results early. With more than 4,000 individuals from more than 23 countries, the randomized clinical trial found that the risk of AIDS, other serious illnesses, or death was reduced by 53% among those who started ART immediately, compared to those who were randomized to only start ART after their CD4 count dropped to 350. The benefits of early treatment were similar for the 2,350 participants from low- and middle-income countries and the 2,155 participants from high-income countries (NIH, 2015). Given these trial results, some have argued that it is duty of all states to provide early access to treatment (Kavanagh et al., 2015). While there are clear individual and public health benefits to early treatment, efforts to promote immediate treatment access must not lose the individual within the larger public health effort and must also take into consideration the issue of autonomy that women living with HIV have consistently raised with respect to healthcare decision-making, including...

“Despite potential individual and public health benefits for women living with HIV, the decision to begin treatment for HIV is a deeply personal decision that reflects a variety of private, contextual and structural factors” (ICW, 2015).
whether and when to start treatment. Rights to bodily integrity and privacy require that people living with HIV control their medical decisions and be provided choice in accessing treatment, rather than becoming targets of human rights violations to ensure they are adherent to ART (Kavanagh et al., 2015). People must be given the right to decline ART until they are ready.

Up until the announcement of the START results, the optimal time to initiate ART had been a subject of considerable debate (Cohen et al., 2011a: 2). Current 2013 WHO treatment guidelines recommend ART for adults with CD4 counts in the 350 to 500 cells/µl range, with priority given to individuals with severe disease or CD4 counts under 350 (WHO, 2013), with revised guidelines expected in 2015. In the United States, ART is recommended as soon as a person tests HIV-positive, regardless of viral load or CD4 count (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013). In Europe, ART is not unconditionally recommended for individuals in the 350 to 500 CD4 count range (Williams et al., 2012 cited in Phillips et al., 2014).

While the START results demonstrate the optimal time to initiate ART, resources to ensure immediate treatment may not be available and current WHO guidelines remain in effect. Clinicians may still have to “balance the risks of delaying antiretroviral treatment against the possible harms associated with premature exposure to HAART, including side-effects, pill burden, cost and potential for avoidable antiretroviral resistance” (Nolan and Wood, 2014: 258).

Concerns have been raised about potential adverse effects, emergence of drug resistance, difficulties in access to second- or third-line ART, and exhausting treatment options if ARVs are initiated early (Socias et al., 2013). WHO guidance (WHO, 2013) provided on initiation is by CD4 count rather than by viral load. WHO notes that viral load monitoring, rather than CD4 counts, is the preferred approach for monitoring once a patient is on ART as this is a better indicator of treatment failure and helps determine if there is a need to switch to a second-line drug (WHO, 2014c; Bonner et al., 2013).

However, a lack of access to viral load monitoring in resource-limited settings may prejudice those who start antiretroviral therapy while asymptomatic and at higher CD4 counts (Gallant et al., 2013). WHO recommends that CD4 counts be used when viral load is unavailable. For countries which cannot reliably implement a deferral strategy for those who test HIV-positive yet have CD4 counts above 500, it “seems prudent to initiate ART almost as soon as a person is first identified by the care services, to decrease the risks of late re-presentation with

“We now have clear-cut proof that it is of significantly greater health benefit to an HIV-infected person to start antiretroviral therapy sooner rather than later...Moreover, early therapy conveys a double benefit, not only improving the health of individuals but at the same time, by lowering their viral load, reducing the risk they will transmit HIV to others. These findings have global implications for the treatment of HIV.”

- Dr. Anthony Fauci, Press release announcing START clinical trial results (NIH, 2015)
advanced HIV symptoms” (Phillips et al., 2014: 940). For countries with limited ART coverage, a priority should be to develop “a deferral strategy though regular CD4+ cell count monitoring in order to allow prioritization of those in most urgent need…” (Phillips et al., 2014: 940).

A lack of lab facilities to measure CD4 counts and viral load monitoring is a major barrier and WHO guidelines must be adapted to country contexts. “Our ongoing scientific and moral challenge will be to continue to narrow the gulf between north and south and to ensure that we do not accept the establishment of two standards of care: one for richer countries and the other for the poorer…” (Granich et al., 2010: para 11). At the same time, “We must not lose sight of the glaring disparities among nations that stand as obstacles to the ethical implementation of early ART” (Gallant et al., 2013: 886).

All guidelines agree that patient readiness is key in deciding when to initiate treatment (NIDA and IAS, 2010). Interviews with people living with HIV in Zambia found that they only sought treatment when symptomatic, which may lead to delays and may present challenges for early initiation of treatment with CD4 counts up to 500 where patients are often asymptomatic (Musheke et al., 2013a).

National governments face dilemmas in how best to increase the numbers of those accessing treatment, maintain quality of care, avert loss to follow up and drug resistance while changing national guidelines to WHO’s 2013 guidance to increase those who can qualify for treatment. Loss to follow up remains a critical problem: a study from South Africa found that rates of viremia were higher among those lost to follow up than for those who remained on care (Stinson et al., 2014), meaning that those who were lost to follow up were more likely to transmit HIV and to suffer mortality and morbidity. Interventions are needed to “overcome the main health system barriers such as an efficient appointment [and] patient monitoring systems and providing after-hours and weekend clinics” (Govindasamy et al., 2014b: 2).

**Universal Access to Treatment Can Be Achieved**

Progress is being made with treatment access: in some settings, patients who were initiated into treatment in more recent years are initiated at higher CD4 counts than in the earlier years of scale-up, and the mortality rate of those initiated has been lowered in more recent years than at the start of scale-up (Mulissa et al., 2010). Universal access to antiretroviral therapy in low-income countries can be achieved. Rwanda attained the UN threshold for universal coverage of ART of 80% in 2009, with long-term retention of care in some studies at 90% (Binagwaho et al., 2014).

However, prevention efforts must continue alongside efforts to expand treatment access (Piot et al., 2015). Anticipating now how best to deliver ART to “the ever growing cohort,” in the context of decreasing donor resources, is needed. Better delivery includes enhancing simplicity, efficacy and cost effectiveness of delivery; designing simpler and cheaper ART protocols that are less toxic and easier for health services and patients; piloting innovative service delivery outside of health services, with community or expert patient-based models; and understanding how to address the gendered dimensions of treatment access and adherence.
(Zachariah et al., 2011b). Remuneration for lay workers in communities is also required (Decroo et al., 2014). Other structural challenges in resource-limited settings include distances to clinics, waiting lines, and drug stockouts. In recent years between 30% and 45% of low- and middle-income countries reported annual ART stock outs (WHO, 2014a). Without adequate infrastructure, the likelihood of developing resistance is increased (Gallant et al., 2013).

How to integrate HIV care into accessible, nonstigmatizing services within national health systems – including for people with HIV and TB or Hepatitis C co-infections – remains an ongoing challenge. [See also Preventing, Detecting and Treating Critical Co-Infections] Concerns have been raised that HIV efforts may shift scarce resources away from other urgent health priorities, rather than create a synergistic effect. “It is still common in Africa to see newly constructed, well-staffed HIV clinics side by side with crumbling primary health care facilities, with little integration and few linkages between services” (Pfeiffer et al., 2010: 2). But integration of HIV care services into primary care systems can simultaneously strengthen both HIV services and the broader system in which these services are embedded. For example, an analysis of 1,538,612 adults, including 60,303 deaths from 41 surveys in 27 countries found that between 2004 and 2008, all-cause mortality declined more in countries which were the focus of PEPFAR efforts (Bendavid et al., 2012a), though “ongoing research is needed to identify best-practice service delivery models” (Filler et al., 2011: e1). [See also Structuring Health Services to Meet Women’s Needs] All those millions of people who do get on treatment will need to continue being treated, cared for and supported for many decades to come (IOM, 2013).

Better systems are needed to reduce attrition (Zachariah et al., 2011a): tracking those who are alive and on therapy; dead; stopped treatment; transferred to another facility; and those who were lost to follow up is vital to gauge program success. A study that assessed outcomes for patients lost to follow up and who were then tracked in 17 studies from sub-Saharan Africa found that combined mortality was 46% (Brinkhof et al., 2009). Uninterrupted ART drug supplies are essential. Linking the data system with drug forecasting and procurement is also needed.

This is a brief overview of key areas in HIV treatment and service delivery and is not meant to provide treatment guidelines. See WHO, 2013 guidelines are available at WHO, 2013: [http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1). New WHO guidelines, expected to be released in December 2015, will update the guidance from 2013 and include new areas such as the use of laboratory diagnostics, improving the quality of care, treatment of other co-morbidities and treatment and delivery of HIV care for adolescents.

**7A. What Works—Treatment: Provision and Access**

1. Antiretroviral therapy has been successfully administered with good adherence, good patient retention, and good clinical outcomes in resource-poor settings, including humanitarian settings, with increased patient survival; results have been similar to those
achieved in resource-rich countries.

2. Early initiation of antiretroviral therapy results in improved quality of life and reduced mortality.

3. Antiretroviral therapy initiated at CD4 counts between 350 and 550 can result in fewer serious HIV-1-related clinical events or death.

4. Integrating CD4 count service with voluntary counseling and testing or primary health clinics can accelerate initiation of treatment.

5. Use of co-trimoxazole prophylaxis together with initiation of antiretroviral therapy decreases mortality significantly.

6. Home- and community-based antiretroviral treatment may be effective, but attention must be paid to the potential effects of stigma and discrimination.

7. Integration of HIV and AIDS services into primary care increases access to testing and treatment services.

A. Evidence

1. Antiretroviral therapy has been successfully administered with good adherence, good patient retention, and good clinical outcomes in resource-poor settings, including humanitarian settings, with increased patient survival; results have been similar to those achieved in resource-rich countries.

   - A systematic review of 69 peer-reviewed papers and 20 abstracts from 2002 to 2010 found that the roll-out of ART treatment was successful in numerous sub-Saharan African countries (Angola, Botswana, Burkina Faso, Cameroon, Côte d’Ivoire, Kenya, Malawi, Mali, Mozambique, Nigeria, Rwanda, Senegal, South Africa, Tanzania, Uganda, Zimbabwe and Zambia) in terms of virological suppression during a two year period. Viral load measurement of at least once after starting ART and minimum follow-up of three months after initiation of ART was required for inclusion. Virological success was considered in patients in whom HIV-1 RNA level was brought down to fewer than 400 copies. Virological failure was defined as viral RNA level of above 1000 copies. Drug resistance reports for sub-Saharan Africa were summarized and mutations were analyzed according to the International AIDS Society 2008 update. Virological data of 63,684 patients from more than 11 sub-Saharan Africa countries’ HIV/AIDS treatment programs were included. The proportion of women patients in most of the studies was above 50%. Eight percent (5,021) of the patients participated in clinical trials. The follow-up period ranged from a three months to 5 years. Most patients started ART at an advanced stage of disease. The HAART regimen for 58,608 (92%) patients was available. Ninety-nine percent of patients were treated with a regimen consisting of two NRTIs with either nevirapine or efavirenz. Only 6% of the patients were on PI based regimen. After six months of ART, virological success was achieved in 10,351 (78%) out of 13,288 patients based on on-treatment analysis. Seventy-six percent (7,413 out of 9,794 patients) had virological success after one year of ART. At 24 months 3,840 (67%) of 5,690 patients had virological success in on-treatment data. Only 5 studies reported virological success data at three years in which it was achieved in 712 (67%) of 1,062 patients. When a lower cut-off value for virological success was used (fewer than 50 copies) the proportion of patients with virological success at 6, 12 and 24 months was 67%, 66% and 67% respectively. These findings were comparable to the data from developed countries. The overall proportion of virological failure was 15%. Eighty percent of the programs with on-treatment analysis and 63% with intention-to-treat achieved the target of virological suppression rate of above 70% at one year after initiation of
ART. However, data to evaluate the long-term success rates is scarce (Barth et al., 2010). (Gray I) (treatment, Angola, Botswana, Burkina Faso, Cameroon, Côte d’Ivoire, Kenya, Malawi, Mali, Mozambique, Nigeria, Rwanda, Senegal, South Africa, Tanzania, Uganda, Zimbabwe and Zambia)

- Data from 5 demographic surveillance sites collecting longitudinal data in Malawi, South Africa, Tanzania, and Uganda found that excess mortality in people living with HIV decreased by over 50% after the introduction of ART; however, mortality rates in adults living with HIV in these communities was still 10 times higher than the mortality rate in the HIV-negative population. Surveillance data was utilized to estimate mortality attributable to HIV before and after ART implementation. HIV-attributable mortality was 45 to 88 deaths per 1,000 person-years before ART introduction, and 14 to 46 deaths per 1,000 person-years after ART introduction. A total of 244,269 adults, of which 127,585 knew their HIV status, contributed 1,149,484 person-years of follow-up. The data was divided between pre-ART introduction (5 years preceding ART introduction), rollout of ART (where ART was assumed to not be fully available), and widespread ART availability. Declines in mortality were seen in all HIV-positive mortality rates, except for men at one site. The HIV-negative mortality changed little over the study period. The greatest reduction in mortality rates was seen in older age groups; in some 15-19 year old cohorts the mortality attributed to HIV increased slightly after ART implementation. However, in the rollout period, the mortality reduction was greatest at younger ages (less than 35 years). After ART was implemented, women below age 30 had higher rates of mortality than men, whereas after age 30, men had higher mortality rates than women. Women over 40 have a mortality risk that was 60% or less of the mortality risk of men. The significant reduction in mortality before and after ART initiation was seen in both men and women. For example, in the cohort in Uganda, the HIV-positive mortality rate for men decreased from 88.0 deaths per 1,000 person-years pre-ART to 43.6 deaths per 1,000 person-years post-ART implementation. For women, the mortality rate decreased from 91.5 deaths per 1,000 person-years pre-ART to 30.3 deaths per 1,000 person-years post-ART implementation. This occurred over a period of time when the HIV-negative mortality rate stayed nearly constant; however, the HIV-positive mortality rate was still significantly higher than the 3.8 and 2.3 deaths per 1,000 person-years for HIV-negative men and women, respectively, post-ART implementation (Slaymaker et al., 2014). (Gray IIIa) (treatment, Malawi, South Africa, Tanzania, Uganda)

- A longitudinal cohort study following 20,000 people in Uganda from 1999 to 2009 found that the introduction of ART resulted in a decrease of overall mortality in adults by 37% in women and 32% in men. The study evaluated the mortality rates of those living with HIV and those who were HIV-negative people before and after the introduction of ART. ART was introduced in January 2004. In addition, the analysis showed a 27-fold increased mortality risk in HIV-positive compared with HIV-negative individuals aged 15-59 before ART, which fell after ART introduction to 21-fold in the first year after introducing ART and fell nine-fold in the subsequent 4 years. The ART period data is divided into the first year after implementation (January 2004 to January 2005), and the following four years (2005-2009). National guidelines had ART initiated when CD4 count dropped below 200 cells/µl. The introduction of ART significantly brought down the rates of mortality among the entire population by lowering mortality rates of those living with HIV. In the five years prior to 2004, when ART was provided, the probability of dying from any cause between age 15 and 60 was 51% for men and 44% for women. In the entire post-ART period, those rates decreased to 38% for men and 32% for women. The pre-ART mortality rate for HIV-negative individuals was 4.0 deaths per 1,000 person-years, while the mortality rate for individuals living with HIV was 116.4 deaths per 1,000 person-years. The mortality rate for individuals living with HIV fell dramatically in the first year after ART was introduced to 87.4 deaths per 1,000 person-years, and the rates decreased further in the following four years to 39.9 deaths per 1,000 person-years. During this time, the mortality rate among the HIV-negative population did not change significantly, and there was no difference in mortality trends between men and women. The impact was greatest among the individuals aged 30-44 years. Further, the drop seen in mortality among this population is associated with the drop in mortality rates among individuals living with HIV once they have access to ART (Kasamba et al., 2012). (Gray IIIa) (treatment, Uganda)
• Serological, behavioral, and demographic surveillance data from 2000 to 2009 study of 30,000 people in Tanzania found that the overall fall in female mortality rates was from 8.8 deaths per 1,000 person years before 2005 (pre-ART) to 6.5 deaths per 1,000 person-years after 2005 (post-ART), nearly a 30% decrease in mortality. The study assessed the impact of free ART on adult mortality rates. Free HIV care including ART has been available in the area since 2005. Analysis of the population before and after the introduction of ART show that for women, the crude death rate fell for both women living with HIV and HIV-negative women. Although the death rate among women living with HIV was much higher than their HIV-negative counterparts, the mortality rate among both groups declined with the introduction of free ART. From 2000 to 2009, the adjusted mortality rate was 10.4 times higher for women living with HIV than for HIV-negative women. The mortality rate among men did not change significantly over the two time periods – at 9.1 deaths per 1,000 person-years in the pre-ART period and 8.5 deaths per 1,000 person-years in the post-ART period. ART uptake among the study population increased steadily after 2005, with the number of women on treatment quadrupling and the number of men on treatment doubling (Marston et al., 2012). (Gray IIIa) (treatment, Tanzania)

• A cohort study conducted with data from six ART programs in South Africa found that patients on ART had life expectancies that were 62-75% of HIV-negative adults, and 70-86% of HIV-negative adults when they started treatment before their CD4 count dropped below 200 cells/µl. Life expectancy was also 15-20% higher in patients who survived 24 months after initiation of ART as compared to patients just starting treatment. The study estimated the life expectancy of patients on ART. The data from 37,740 adults who started ART between 2001 and 2010 was analyzed. ART was initiated when the patient’s CD4 count dropped below 200 cells/µl or when the disease had progressed to the clinical stage IV. Individuals were grouped into CD4 count categories at initiation: less than 50 cells/µl, 50-99 cells/µl, 100-199 cells/µl, and more than 200 cells/µl. A total of 2,066 deaths were recorded in the patient record system, and 16,250 patients were lost to follow-up. Of the 16,250 patients lost to follow-up, 13,968 were in the national population register and 2,947 deaths were recorded through this method. In total, there were 5,782 deaths in 69,514 person-years of follow-up. A recorded 13.2% of patients had initial CD4 counts above 200 cells/µl, and 61.5% of the patients were women. The mortality rate was 99.8 per 1,000 person-years for men and 72.6 per 1,000 person-years for women. Mortality rates were highest in the first year of treatment. The most significant factor determining life expectancy of treated patients was age at ART initiation. A man starting treatment at age 20 had an average of 27.6 additional years while a man starting treatment at age 60 had an average of 10.1 additional years. A woman starting treatment at age 20 had an average of 36.8 additional years while a woman starting treatment at age 60 had an average of 14.4 additional years. Patients who had initial CD4 counts of below 50 cells/µl had life expectancies that were 48-61% of those of HIV-negative adults, a significant reduction as compared to patients who initiated treatment at higher CD4 counts. Patients who started treatment after 2006 also had higher life expectancies than patients who started ART in 2006 or before (Johnson et al., 2012). (Gray IIIb) (treatment, life expectancy, South Africa)

• A cohort study to determine the effects of the provision of ART on adult life expectancy was conducted from 2000 to 2011 in South Africa and found that adult life expectancy increased from 49.2 years in 2003 (the year before ART was introduced) to 60.5 years in 2011. This 11.3-year gain can mostly be attributed to the introduction of ART as data collected on non-HIV-related (HIV-cause-deleted) adult life expectancy remained almost constant over the entire study period. Based on the standard monetary valuation of life, the provision of ART was found to be very cost-effective. The study included a total of 101,286 people, of whom about 60,000 were 15 years old or older at any given time and therefore included in the biannual household survey. During this study period, 29% of adults were living with HIV in the geographic area. Over half of women ages 25-29 and over 40% of women and men 30-34 were living with HIV. Before the introduction of ART, over half of all deaths were attributed to HIV. From 2000 to 2003, the adult life expectancy decreased from 55.4 to 51.3 years for women and from 49.0 to 46.9 years for men. In 2004, South
Africa began to provide ART to adults with a CD4 count below 200 cells/µl. In 2010, eligibility for ART was extended to HIV-positive pregnant women and patients with active TB with CD4 counts below 350 cells/µl, and in 2011 these eligibility requirements were extended to all HIV-positive patients. From 2004 to 2011, the adult life expectancy increased to 64.5 for women and 55.9 for men. Verbal autopsy data was also collected to estimate HIV-cause-deleted adult life expectancy. This measure, when compared to the standard adult life expectancy, showed the effects of a particular condition (in this case, HIV/AIDS) on life expectancy as a whole. The HIV-cause-deleted adult life expectancy did not change significantly from 2000 to 2011, which shows that the changes in the overall life expectancy could be largely attributed to HIV and the implementation of ART. The cost-effectiveness ratio was $1,593 per life year saved, less than a quarter of South Africa’s 2011 per-capita gross national income, making this intervention very cost-effective (Bor et al., 2013). (Gray IIIb) (treatment, life expectancy, South Africa)

- A review of 14 studies found that providing ART in humanitarian settings, while challenging, is feasible, with a pooled mortality of 7.6% at six months and 9% at we months. Loss to follow up at six months was 6.3% at 12 months was 8.1%. Mortality, loss to follow up and adherence was comparable to stable settings. Six studies were carried out in armed conflict settings; five studies reported outcomes from a setting of post-election violence and three studies from natural disaster settings. Studies took place in Burkina Faso, Democratic Republic of Congo, Ghana, Kenya, Thailand, Côte d’Ivoire, Uganda, India, Sudan, and Haiti. No studies reported virological suppression as an outcome (Griffiths and Ford, 2013). (Gray IIIb) (treatment, displaced persons, conflict, Burkina Faso, Democratic Republic of Congo, Ghana, Kenya, Thailand, Côte d’Ivoire, Uganda, India, Sudan, Haiti)

- A cohort study was conducted in Myanmar (Burma) from 2003 to 2009 in an ART program headed by Médecins Sans Frontières (MSF) and found that 72% of patients were retained in care at 5 years following initiation; 13.8% of the patients died and 6.5% were lost to follow-up over the study period. Attrition (death and loss to follow-up combined) was nearly 4 times higher in the first 6 months than in the following period of 7-36 months. Older age, being a man, WHO stage IV disease at initiation of ART, and body mass index (BMI) of less than 16 kg/m² were all predictive of attrition. The study followed all adult patient who initiated ART in the program between 2003 and 2007, a total of 5,963 adults with 17,581 person-years of follow-up. The median age of patients at baseline was 33 years, 61% were men, and 45% were in WHO stage IV. For those with a CD4 count available, the median CD4 count was 71 cells/µl. Medical professionals as well as lay counselors and support workers provided services. Adherence support was provided at the clinic and in the community by outreach workers. Local food support was provided for the first 6 months of treatment and exceptional cases (patients with disabilities) were provided financial support for transportation. CD4 testing was limited throughout the study period; therefore ART was initiated based on WHO clinical staging criteria alone. The strongest predictor of attrition was BMI of less than 16 kg/m²; these patients were lost from the program at more than 4 times the rate of those with a normal BMI (Sabapathy et al., 2012). (Gray IIIb) (treatment, Myanmar)

- A study in Uganda conducted with HIV-positive adults who were lost to follow-up to determine the rates of mortality, loss to follow-up, and transfer of care among all those classified as lost to follow-up after being enrolled in care at a CD4 count higher than 350 cells/µl and being unable to initiate ART found that more than half of the patients who were tracked down were retained in care at another facility, whereas slightly less than half were not retained in care. There were 6,473 patients who made a visit to one of two clinics in the study between 2008 and 2011 who were enrolled in care at CD4 counts of more than 350 cells/µl. One thousand ninety-four patients (20%) were lost to follow-up. In this sample, 71% were female, the median age was 29 years old, and the median CD4 count was 550 cells/µl. A random sample of the patients lost to follow-up was sought in the community by peer educators. They were to measure the patients’ vital statistics and current care status. Patients were considered to be retained in care if they had seen a doctor or nurse for HIV care in the last 6 months. Two hundred and seven (16% of those lost to follow-up) were
randomly selected to be sought in the community. Of those patients who were interviewed directly, 51% were seeing a provider at a new clinic and 49% were no longer seeing an HIV provider. For those patients no longer in care, the most commonly reported reasons was that work responsibility kept from them seeking care or that they had moved to an area not serviced by an HIV clinic. For those that had transferred care, the most commonly reported reasons were that the new clinic was closer to their home or work, that they preferred the new clinic, or that they had a conflict with the staff at the clinics under study. Of those lost to follow-up with updated information, 11% had died. Among the patients lost to follow-up, 35.4% had initiated ART after 2.5 years. The rate of death increased over time for patients enrolled in care with CD4 counts of more than 350 cells/µl, from 0.6% at 1 year, to 1.6% at 2 years, and 2.5% at 2.5 years. The recorded retention in care for these clinics was 69.5% in the 2.5 years measured. However, when the proportion of patients who were retained in care through other clinics is added, the retention in care measure rises to 88.2%. These numbers demonstrate that reported numbers of lost to follow-up for those with CD4 counts above initiation levels may be misleading and that transfers in care may be a significant proportion of patients who are classified as lost to follow-up (Namusobya et al., 2013). (Gray IIIb) (treatment, Uganda)

- A study in South Africa of 3,162 patients initiated on ART found that patients had a one year mortality rate of 7.9% despite many having advanced immunodeficiency, with CD4 counts at initiation at 87 in the period 2002-2004 and 121 in the period from 2007 to 2008. The cumulative probability of death after six years was 15.2%. In addition, over 93% of patients had excellent virological suppression of under 400 copies per milliliter at 16 weeks but the probability of virological failure in the whole cohort of all patients at six years was 23.1% (Nglazi et al., 2011). (Gray IIIb) (treatment, CD4 counts, South Africa)

- A retrospective longitudinal study in Ethiopia of 37,466 patients from 30 hospitals and 25 health centers which provided ART for more than 200 patients by 2008 found that the median CD4 count was 125 when patients were initiated on ART and increased to CD4 counts of 242 at six months, 269 at 12 months and 316 after 24 months on ART. The number of patients on ART increased from 900 in 2005 to 180,000 by the end of 2008. However, after 24 months on ART, health facilities retained only 68% of their patients (Assefa et al., 2011b) (Gray IIIb) (treatment, CD4 counts, Ethiopia)

- An observational study done in Chile found that expanded access to ART improved survival of patients in the long term. A total of 5,115 ART naïve patients (26% women) were followed between 2002 and 2007. At 12 months, 72% of the patients were alive and maintained on the first line-regimen. Virologic suppression at last visit was 73.4% for the 94.8% of patients who had viral load results available. Survival rate was 88.4% at the end of the six-year follow-up period. The mortality rate was 2.55 per 100 patient-years. Inferior survival rates were noted in patients who started ART at a lower CD4 cell counts or at advanced clinical disease (Wolff et al., 2010). (Gray IIIb) (treatment, CD4 counts, Chile)

- A study using routinely collected program data from 2004 to 2005 of 972 patients at three government clinics in India found that of the 927 patients for whom treatment outcomes were available, 71% were alive after two years of treatment. The majority of deaths occurred within the first six months of treatment (Bachani et al., 2010). (Gray IIIb) (treatment, India)

- Data from the Ministry of Health, Jamaica found that public access to antiretroviral therapy (ART) in 2004 coupled with improved lab capacity and support services resulted in a 40% decreased in AIDS deaths between 2004 and 2008 (Duncan et al., 2010a). (Gray IIIb) (treatment, Jamaica)

- A systematic comparison of antiretroviral therapy on mortality of HIV-positive patients in both low-income and high-income countries found that antiretroviral therapy is feasible and effective in low-income settings. Mortality was higher in the first few months of treatment for patients in low-
income settings. Those in low-income settings started treatment with considerably more advanced immunodeficiency than those from industrialized countries, but virological and immunological response to HAART were similar in both settings. The study compared 4,810 treatment-naïve adult patients (51% female) from 18 HAART programs in Africa, Asia and South America (low-income settings) with 22,217 treatment-naïve adults (25% female) in 12 HIV cohort studies from Europe and North America (high-income settings) and compared baseline characteristics and outcomes during the first year of HAART (Braitstein et al., 2006). (Gray IIIb) (treatment, HAART, Africa, Asia, South America, Europe, North America)

2. Early initiation of antiretroviral therapy results in improved quality of life and reduced mortality.

- A review by WHO of one randomized controlled trial and 13 observational studies from the USA and other developed countries found a decreased risk of death in persons who initiated ART at CD4 counts of at least 350 (Anglemyer et al., 2014). (Gray I) (treatment, CD4 counts)

- A Cochrane review that analyzed data from two randomized clinical trials found that initiation of ART at CD4 levels above 200 or 250 reduced mortality. A combined total of 1,065 ART naïve, asymptomatic adults above 15 years of age were included in the analysis. Risk of death was reduced by 74% in patients who initiated ART at CD4 counts at 350 (SMART 2008) or between 200 and 350 (CIPRAHT001-Haiti). Risk of TB was reduced by half in the group of patients starting ART at levels above 200 or 250 and at 350. In the SMART study sub-group (249 patients), starting ART when patients had CD4 counts of 350 rather than waiting until the CD4 count decreased to 250 reduced the risk of disease progression by 70% (Siegfried et al., 2010). (Gray I) (treatment, CD4 counts, TB)

- A randomized clinical trial with 4,685 men (half MSM) and women (27% women) above age 18 found that over an average of three years, the risk of AIDS, other serious illnesses or death was reduced by 53% among those who started ART immediately (41 events of AIDS, other serious illnesses or death) compared to those who were randomized to only start ART after their CD4 count dropped to 350, (86 events). The benefits of early treatment were similar for the 2,350 participants from low- and middle-income countries and the 2,155 participants from high-income countries: (USA, Europe, Australia, Argentina, Brazil, Chile, Czech Republic, Estonia, India, Malaysia, Mali, Mexico, Morocco, Nigeria, Peru, Poland, South Africa, Thailand and Uganda). The risk of developing serious non-AIDS related events, such as hospitalizations, quality of life, etc., was also lower in the early treatment group compared to those patients who started ART at CD4 counts below 350. Participants with a CD4 cell count of over 500 were randomized to one of two equal sized groups, where one group initiates ART immediately and the other initiates ART once the CD4 count has decreased to under 350. The original sample size was increased to 4,600 because the baseline CD4 count was much greater than originally assumed (median CD4 cell count about 650 compared with 566 cells as originally assumed) (The INSIGHT Strategic Timing of Antiretroviral Treatment (START) Study Group, 2015). (Gray II) (treatment, CD4 counts, USA, Europe, Australia, Argentina, Brazil, Chile, Czech Republic, Estonia, India, Malaysia, Mali, Mexico, Morocco, Nigeria, Peru, Poland, South Africa, Thailand and Uganda)

- A follow-up study on the HPTN 052 randomized control trial (Cohen et al., 2011a) and found that early initiation of ART delayed the time to, and significantly reduced the incidence of, AIDS-defining events, tuberculosis, and WHO stage 2 and 3 events. A group of 1,763 HIV-positive people with a serodiscordant partner from sites in Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, and Zimbabwe were randomly assigned to early ART treatment or to delayed treatment. Eight hundred eighty-six were assigned to the early treatment group (initiation of ART at enrollment) and 877 were assigned to the delayed treatment group (initiation when CD4 dropped below 250 cells/µl or with the development of an AIDS-related illness). The median age of the participants was 33 years, half the study population were women, and the median baseline
CD4 count was 436 cells/µl. The median CD4 count at initiation of ART for the delayed treatment group was 230 cells/µl. The cumulative probability for developing a primary outcome event over 2 years was 4.8% in the early treatment group and 7.9% in the delayed treatment group. Primary outcomes included death, onset of WHO stage 4 disease, development of tuberculosis, bacterial infections, serious cardiovascular events, liver and renal disease, development of diabetes, and non-AIDS defining malignant diseases. There was no difference in development of a primary outcomes between the early and delayed treatment groups when the data was stratified by age, geography, sex, and baseline CD4 count. The cumulative probability of having an AIDS event over 2 years was 3.3% in the early treatment group and 6.0% in the delayed treatment group. The cumulative probability of developing tuberculosis over 2 years was 1.2% in the early treatment group and 3.7% in the delayed treatment group. The study, however, “did not record an effect on all cause mortality,” (Grinsztejn et al., 2014: 9). Secondary outcomes were also measured, which included stage 2 and 3 events and other conditions including malaria, chronic renal insufficiency, and hypertension (among others). In total, 34% of patients in the early treatment group and 36% of patients in the delayed treatment group experienced secondary outcomes. Primary and secondary outcomes were not concentrated among participants with low CD4 counts; most events were recorded when the most recent CD4 count was higher than 350 cells/µl. Overall, 24% of patients in the delayed treatment group ultimately began ART. The median change over 2 years in CD4 count for the early treatment group was an increase of 225 cells/µl, while the median for the late treatment group was a decrease of 37 cells/µl. After treatment was initiated, the median change over 2 years in the late treatment group was an increase of 246 cells/µl. Although the increase was similar in both groups, the initially lower CD4 cell counts for patients in the delayed treatment group did not reach the same levels as the early treatment group reported, which may suggest that delayed treatment can impede or curtail restoration of immunity (Grinsztejn et al., 2014). (Gray II)

**Note:** Others argue that HPTN 052 cited here was not powered to examine mortality (De Cock and El-Sadr, 2013a). (treatment, Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, and Zimbabwe)

- A randomized controlled trial conducted in Haiti showed that earlier initiation of antiretroviral therapy improved the rate of survival and quality of life of patients. A total of 816 patients (58% women) with CD4 counts between 200 and 350 were recruited between 2005 and 2008 and followed for a total of nearly two years. Patients were randomized to 1) a treatment group in which ART was initiated within two weeks of enrollment to the study, referred to as the early treatment group; or 2) deferred in accessing ART until their CD4 count fell at or below 200 or until an AIDS defining illness developed according to the national guideline at the time (standard treatment group), referred to as the standard treatment group. Only 1% in the early treatment group died compared to 6% in the standard group in the median 21-month follow-up. At 36 months 98% of the participants in the early treatment group were alive versus 93% in the standard treatment group. The risk of dying for a patient in the standard treatment group was four times greater than those in the early treatment group. There was only one death from infectious cause in the early treatment group compared to 17 in the standard treatment group. A fifty percent reduction in the incidence of tuberculosis was also noted in the early treatment group (Severe et al, 2010). (Gray II) (treatment, CD4 counts, TB, Haiti)

- Data from the CAPRISA 002 cohort study following women living with HIV in South Africa found an improvement in overall quality of life, and in the sub categories of physical well-being, emotional well-being, and social well-being with the initiation of ART. No negative impact was found on the other two quality of life measurements recorded in the study (functional and global well-being and cognitive functioning). This study included a group of 160 women living with HIV recruited in 2004 and followed for up to nine years. Participants completed a baseline assessment when enrolled in the study, which included the Functional Assessment of HIV Infection. The assessment measured self-reported quality of life under five subcategories: physical well-being, emotional well-being, function and global well-being, social well-being, and cognitive functioning. For all participants, this assessment was done at baseline, at three months, and then biannually.
Through the period of follow-up, 51 of the 160 participants initiated ART following South African guidelines. Of the ART cohort, the mean age was 25.9 years old, 75% were married or had a stable partner, and 13.7% reported being involved in sex work. The mean CD4 count was 488 cells/µl at enrollment. Comparisons between the ART and the non-ART group showed that the self-reported quality of life was higher in the group of women on ART. About one-third of women in the ART group had long-term gains in quality of life after they initiated ART. Stable partnership was also strongly associated with high self-reported quality of life (Tomita et al., 2014a). (Gray IIIa) (treatment, quality of life, South Africa)

- A retrospective cohort study from 2001 to 2010 in four HIV programs in Malawi, Uganda, and Kenya supported by Médecins Sans Frontières (MSF) found that patients with a CD4 count falling below 500 cells/µl experienced higher mortality than patients with a CD4 count consistently above 500 cells/µl. A total of 24,037 patients were followed for 69,516.2 person-years of follow-up. Of these patients, 68% were women, 2.4% died, and 10.3% were lost to follow-up. CD4 counts were measured upon initiation of ART and were routinely monitored every 6-12 months. CD4 counts were classified in five categories: less than 50, 50-199, 200-349, 350-499, and 500 cells/µl or more. The study found higher survival rates of patients at each higher increment of immune response. The mortality rates were 0.36 deaths per 100 person-years for a CD4 count of at least 500 cells/µl, 0.58 deaths per 100 person-years for 350-499 cells/µl, 0.88 deaths per 100 person-years for 200-349 cells/µl, 1.91 deaths per 100 person-years for 50-199 cells/µl, and 7.43 deaths per 100 person-years for less than 50 cells/µl. The study also found that women had better survival rates than men. Without the extra support of MSF, “the survival benefit achieved by reaching 500 CD4 cell counts would be even higher,” among other sub-Saharan public health programs (Maman et al., 2012a: 1397). (Gray IIIa) (treatment, mortality rates, Malawi, Uganda, Kenya)

- An observational study in Sub-Saharan Africa, with 22,315 patients (69.4% women) who started antiretroviral therapy between January 2000 and 2010 in Uganda found that likelihood of survival increased in patients with higher CD4 counts on initiation of treatment. Baseline CD4 counts were categorized into seven groups, with the lowest CD4 count of less than 50 and the highest CD4 count of at least 300. The Ugandan cut-off for initiation of antiretroviral therapy was a CD4 count under 250. The study showed the highest mortality among patients whose CD4 count was less than 50 at initiation of therapy (risk of dying was 75% likely compared to 41% for those with at least 250 cells). The highest death occurred in the first year of initiation of antiretroviral therapy in all categories. Survival generally decreased with CD4 count and the difference was significant between categories over time (Mills, et al., 2011b). (Gray IIIa) (treatment, CD4 counts, Uganda, Sub-Saharan Africa)

- A study conducted in Brazil found that timely entry to HIV care and treatment reduced mortality. Between 2003 and 2006, 115,369 adults living with HIV were included in the study. A total of 32,602 (28.3%) had CD4 counts under 200 among whom 9,870 (30.3%) had an AIDS defining illness and 12.5% died soon after entry in to HIV care. Late entry to care (i.e. CD4 counts under 350 or an AIDS-defining illness even if CD4 count was above 350) was observed in 43.6% of the patients. A total of 18,002 (15.6%) patients died in the first 12 months of HIV care, which is a 16.5% probability of death from AIDS in the first 12 months of HIV care. Ninety-six percent of the deaths occurred in the first 6 months of treatment. With increased duration of treatment death rates were observed to decrease. Nearly all the deaths (97.5%) occurred among patients who entered into HIV care late. The probability of death in the first 12 months was 36.3% for patients who entered into care late compared to 1% for patients who gained timely access to HIV care. Of the total 18,002 deaths that occurred in the first year, 17,189 could have been avoided had the patients entered into HIV care while still in the early stages of HIV infection (an attributable risk of 95.5%). The estimated number of avoidable deaths corresponded to 39.5% of the total number of deaths (43,523) recorded in the 4 year period. Annual decrease in late entry to care was observed subsequently decreasing the risk of death in the first 12 months from 20.3% in 2003 to 12.5% in 2006. When asymptomatic individuals with CD4 counts 200 to 350 were included, the number of
deaths increased by 249 but the probability of death from AIDS in the first 12 months of care decreased to 27.6% for individuals who entered care late and to 0.6% for those who had timely access to HIV care. The risk of death attributable to late entry into HIV care increased to 97.2%. The results showed that death from AIDS in the first 12 months was strongly associated to late entry into HIV care. Late entry to HIV care increased AIDS mortality rates by more than one-third (Grangeiro et al., 2011). (Gray IIIa) (treatment, CD4 count, Brazil)

- A study conducted between 2006 and 2010 in Lesotho with 1,177 patients (67% women) found that initiating antiretroviral therapy at CD4 counts above 200 decreased the number of deaths, hospitalization and loss to follow-up. Outcomes were assessed based on baseline CD4 count at initiation of antiretroviral therapy. Five hundred and thirty eight patients were initiated when their CD4 count was 200 or less and 639 were initiated on antiretroviral therapy when their CD4 count was greater than 200. Patients who were started on antiretroviral therapy when their CD4 counts were above 200 were 68% less likely to die and 39% less likely to be lost to follow-up compared to those started who initiated treatment when their CD4 counts were below 200. The study also found that early initiation of antiretroviral therapy was associated with a 27% risk reduction of morbidity from diseases such as TB, cryptococcal meningitis and diarrhea. Patients who initiated antiretroviral therapy at CD4 counts above 200 had a 63% decreased risk of hospitalization by 63% (Ford et al., 2010b). (Gray IIIa) (treatment, CD4 counts, Lesotho)

- A study of adults on ART in South Africa, initiated between 2004 and 2012, found a 46% decrease in early mortality (defined as within 91 days of ART initiation) or those who initiated ART between 2011 to 2012, when CD4 counts rose to 199 cells, as compared to earlier years, when median CD4 counts were 110 until 2010, then 145 cells in 2011 and 317 by 2012, once ART eligibility criteria changed to CD4 counts of 350 in 2011. Almost half of the adults who enrolled into care between 2011 and 2012 had a CD4 count above 350. Patients enrolled in more recent years also had lower rates of CD4 cell counts under 50. Patients with CD4 cell counts under 50 had a four fold increased risk of early mortality compared with CD4 cell counts of 201-350. Men had higher early mortality. The study was based on a review of 19,080 patients, 67.6% female. Of those who die within the first year of ART initiation, 60% die within the first three months (Lessells et al., 2014). (Gray IIIb) (treatment, mortality rates, South Africa)

The Temprano randomized trial was done in Côte d’Ivoire on 2,076 people from 2008 to 2015. The study was evaluating the effects of immediate ART initiation as compared to initiation according to WHO criteria, as well as the use of Isoniazid preventive therapy (IPT). The study found that early initiation of ART reduced the risk of severe morbidity by 44% and that IPT reduced the risk of severe morbidity by 35%. The WHO recommends that people living with HIV who do not have active TB receive IPT to reduce the incidence of TB. The participants were randomized into four groups: ART initiation with WHO criteria, 6-month course of IPT and ART initiation with WHO criteria, immediate initiation of ART, and 6-month course of IPT with immediate initiation of ART. The participants were 78% women, had a median age of 35 years, and a median CD4 nadir of 465 cells/µl. Upon entering the study, no participants were eligible for ART according to WHO guidelines. Only 2.2% were lost to follow-up. In this study, immediate initiation of ART and IPT significantly decreased mortality for those living with HIV (Danel et al., 2015). (Abstract) (treatment, preventive therapy, tuberculosis, Côte d’Ivoire)

3. Antiretroviral therapy initiated at CD4 counts between 350 and 550 can result in fewer serious HIV-1-related clinical events or death.

- A randomized trial of 1,763 couples in nine countries – Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand and the US - in which one partner was HIV-1-positive and the other was HIV-negative, with 50% of infected partners men, found that early initiation of antiretroviral therapy at CD4 counts between 350 and 550 in 886 couples was associated with a
relative reduction of 41% in the number of HIV related clinical events, which “suggests a clinical benefit for the initiation of antiretroviral therapy when a person has a CD4 count of 350 to 550 cells per cubic millimeter, as compared with therapy that is delayed until the CD4 count falls into the rage of 200 to 250 cells per cubic millimeter (Cohen et al., 2011a). (Gray II) (treatment, CD4 counts, Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand, United States)

• A review of 860 patients on ART from 1996 to 2006 in Côte d’Ivoire for a total of 2,789 person years found that rates of death or AIDS in patients with CD4 counts of 350-499 resulted in a decreased rate of mortality, with 10.4 deaths per 100 person-years at CD4 counts between 200 to 349 and 1.6 deaths per 100 person years at CD4 counts of 350-499. However, the rates of death or AIDS in patients with CD4 counts remained substantial and were higher than those reported from Western Europe (Anglaret et al., 2012). (Gray IIIa) (treatment, CD4 counts, Côte d’Ivoire)

• An analysis of 17,517 asymptomatic patients with HIV infection in the United States and Canada who received medical care from 1996 to 2005 that compared HAART initiation when CD4 count was between 351 to 500 cells/mm$^3$ as compared to greater than 500 cells/mm$^3$ found that among patients who waiting to initiate treatment until their CD4 counts were between 351 to 500 cells/mm$^3$, there was an increase in the risk of death. In the first analysis with 8,362 patients, among patients in the deferred therapy group there was an increase in the risk of death of 69% as compared with that in the early therapy group, after adjustment for calendar year, cohort of patients and demographic and clinical characteristics. In the second analysis involving 9,155 patients, there was an increase in the risk of death of 94%. Female sex was associated with an increased risk of death, but the risk was not significant after adjustment for RNA level, a history of injecting drug use or presence of HCV. The benefits of initiating antiretroviral therapy earlier after HIV infection will need to be weighed against adverse effects of treatment (Kitahata et al., 2009) (*Note that study authors receive consulting fees from many of the companies who manufacture and market antiretroviral therapy drugs. The funding for the study, however, came from NIH and other US government agencies.) (Gray IIIa) (treatment, CD4 counts, HAART, United States, Canada)

• An analysis of multiple cohort studies from Europe and North America showed that patients who initiated ART at CD4 counts of 350 or above had improved survival rates. A total of 45,691 patients of whom 26% were women were followed for those prior to access to ART and those who had access to ART. CD4 counts of patients ranged between zero and 550. Among the 24,444 patients who started ART, 37% started ART when their CD4 counts were between 201 and 350 cells and 21% started ART when their CD4 counts were above 350. Patients who were started on ART when their CD4 counts were between 351 and 450 had improved survival rates compared to patients who initiated ART when their CD4 counts were between 251 and 350. Patients who started antiretroviral treatment when their CD4 counts were between 51 and 150 were 5.67 times more likely to die or progress to AIDS than patients who initiated on ART when their CD4 counts were between 351 and 450 (When To Start Consortium, 2009). (Gray IIIa) (treatment, CD4 counts, Europe, North America)

• An observational cohort study done in Europe, Australia and Canada found that initiation of HAART for individuals at CD4 counts of 350 to 500 was associated with slower disease progression. A total of 9,455 (22.1% women), ART naïve, AIDS-free individuals with CD4 under 800 cells were followed between 1996 and 2009. A cohort study was imagined in which subsequent disease progression of individuals who initiated HAART during a specific month was compared with that of patients who did not initiate HAART during this month. The survival times of patients who deferred HAART in the index month were used to represent the average population prognosis of individuals who were AIDS free and HAART naïve with a CD4 cell count in a specified stratum (0-49 cells, 50-199 cells, 200-349 cells, 350-499 cells or 500-799 cells). During the follow-up period 812(8.6%) patients developed AIDS and 544(5.8%) patients died. Initiating HAART at a given month when CD4 drops under 350 was protective compared to deferring HAART. The study found that at CD4 counts 350 to 499 there was a 25% reduction in the risk of death or progression
to AIDS and a 49% reduction in mortality from all causes. There was no observed benefit of initiating HAART at CD4 counts 500 to 799 cells. The estimated number of patients who needed to be treated to prevent 1 death or AIDS decreased from 79 to 16 at 5 years. Risk reduction was one third as large for patients with CD4 counts of 350 to 499 (Writing Committee for the CASCADE Collaboration, 2011). (Gray IIIb) (treatment, CD4 counts, HAART, Europe, Australia, Canada)

- A retrospective observational cohort study done in the United States found that the optimal time for ART initiation to maximize patient health measured in terms of quality of life was to initiate ART at CD4 counts under 554. A total of 1,034 patients of whom 27% were women were followed between 1998 and 2007. At entry of the study patient’s CD4 counts ranged between 200 and 700. Sixty percent of patients started ART during follow-up. Outcome was measured either based on CD4 count or quality of life measured in terms of AIDS events, death, non-AIDS events and CD4 counts if asymptomatic. The study estimated that one year after a patient entered the study, patient health was maximized by starting ART within 3 months of first CD4 measurement below 554 for those patients for whom outcome was measured based only on CD4 counts. For whom quality of life was the patient outcome, patient health was maximized by initiating ART at CD4 counts of 354. The study also showed that those with pre-ART CD4 counts above 500 generally preferred initiating ART at slightly lower CD4 counts (Shepherd et al., 2010). (Gray IIIb) (treatment, CD4 counts, United States)

4. Integrating CD4 count service with voluntary counseling and testing or primary health clinics can accelerate initiation of treatment.

- A review was done on 15 studies published from 2011 to 2013 in South Africa, Mozambique, Cameroon, Uganda, Tanzania, and Zimbabwe on point-of-care CD4 testing. Compared with lab-based testing, point-of-care CD4 testing increased the probably of a patient having their CD4 count measured and of receiving the results of that test. Time to being tested, as well as time between testing and receipt of result, was significantly reduced. When considering all the data, ART initiation rates were higher when point-of-care CD4 testing was utilized; however, when limited to studies reporting ART initiation by eligible individuals, a statistically significant relationship was not demonstrated. The review included studies on adults, adolescents, children, and pregnant women. There was one randomized controlled trial, one non-randomized trial, 11 observational cohort studies, one retrospective cohort, and one cross-sectional study. The review focused on the proportion of patients in care at each step of the care pathway, and the time it took to reach different levels of the pathway. The steps evaluated included: (1) HIV diagnosis to CD4 testing; (2) CD4 testing to delivery of CD4 results; and (3) eligibility assessment to ART initiation for eligible individuals. The CD4 count cutoff for ART initiation ranged from 200 to 350 cells/µl (except notably in a study including children under 3, where the initiation cutoff was 750 cells/µl). Among the studies reporting on time between HIV testing and eligibility assessment, the probability of CD4 testing occurring was four times higher when point-of-care CD4 testing occurred, as compared to lab-based testing. The probability of patients receiving their CD4 result also increased by nearly a factor of 3. Six studies reported on the proportion of people who initiated treatment after CD4 testing. In the randomized trial, patients receiving point-of-care testing were 3 times more likely to initiate ART than those who received lab-based CD4 testing. A cohort study found that patients were 6 times more likely to initiate ART after point-of-care CD4 testing was introduced, as compared to before introduction when lab-based testing was standard of care. In all studies reporting on initiation of care after CD4 testing, there was either improved rates of initiation, or no statistically significant difference between point-of-care and lab-based CD4 testing. When considering all of the data, ART initiation was more likely among the patients tested with point-of-care CD4 testing; however, when limiting the data to only those studies that reported eligibility of all individuals, there was no statistically significant relationship between initiation of ART and point-of-care CD4 testing. The reduction in time to ART initiation with point-of-care CD4 testing was statistically significant in one of the two studies reporting data on it. This review
also notes that simplicity of point-of-care CD4 testing, which was successfully used in five studies in rural locations and in at least one study by non-physician clinicians (Wynberg et al., 2014). (Gray I) (treatment, CD4 count, health facilities, South Africa, Mozambique, Cameroon, Uganda, Tanzania, and Zimbabwe)

• A study in South Africa which randomized 344 patients, 64.5% female, to three arms found that receipt of CD4 result at the time of HIV diagnosis were 2.6 times more likely to report for ART initiation and 2.1 times more likely to enroll for ART. Other patients received standard of care, i.e. receipt of CD4 results one week after HIV counseling and testing; or CD4 results one week after HIV testing and counseling plus an informational leaflet. ART initiation was measured by arrival at pre-ART care site within one month of HIV testing or for ART initiation within three months if CD4 counts were over 215. Of the patients that received their CD4 counts immediately following HIV testing and counseling, 47.6% reported for further care (pre-ART and ART), where as to those who received their CD4 counts one week later, 33.6% reported for further care. However, for patients not yet eligible for ART, knowledge of a CD4 count immediately after diagnosis did not increase the numbers who enrolled in pre-ART care (Faal et al., 2011). (Gray II) (treatment, CD4 count, health facilities, South Africa)

• Data analysis of 19,525 Thai clients who had HIV testing at a VCT center in Thailand from 2006 to 2009 found that of the 13.2% clients who tested HIV-positive for the first time, CD4 measurements were performed in 73.3% of clients living with HIV at the same center where they had their HIV test and 91.4% occurred within the first month of HIV diagnosis. CD4 count measurement was available to clients at the same VCT center where they had their HIV test. Of the Thai clients, 31.8% were women, and 13.2% of these women tested HIV-positive. “The much shorter duration between CD4 count measurement and HIV diagnosis shown in our study might be the results of our routine posttest counseling which always includes the recommendation of immediate CD4 count measurement in the same clinic” (Phanuphak et al., 2011: 250). Treatment prior to CD4 counts of below 300 increases the risk for mortality (Kitahata et al., 2009; Phanuphak et al., 2011). (Gray IIIb) (treatment, CD4 counts, HIV testing, health facilities, Thailand)

• In Mozambique, following the introduction of point-of-care CD4 testing, the proportion of patients lost to follow up before completion of CD4 staging dropped from 57% (278 out of 492 patients) to 21% (92 out of 437 patients). The median time from enrollment to antiretroviral therapy initiation was reduced from 48 days to 20 days. The study was conducted at four primary health care clinics. Total losses between enrollment and antiretroviral therapy initiation dropped from 64% to 33%. After implementation of point of care CD4 testing, the proportion of enrolled patients who initiated ART increased from 12% to 22%. The median time between enrollment and completion of CD4 staging dropped from 32 days to 3 days (Jani et al., 2011). (Gray IIIb) (treatment, CD4 counts, health facilities, Mozambique)

5. Use of co-trimoxazole prophylaxis together with initiation of antiretroviral therapy decreases mortality significantly.

• A meta-analysis including studies published from 2007 to 2010 with data from Cambodia, Ethiopia, Malawi, South Africa, Uganda, and Zimbabwe examined the effect of daily prophylactic co-trimoxazole on mortality in HIV-positive populations. The analysis found that co-trimoxazole significantly increases the survival rate of HIV-positive individuals on ART. Individual studies also demonstrated a reduction in the cases of malaria and diarrhea, a reduction in the cases of new or recurring WHO stage III or IV disease events, and a reduction in all-cause morbidity. The hazard ratio associated with prophylactic co-trimoxazole was 0.42, as compared to a group on ART who did not take co-trimoxazole. Co-trimoxazole contains two antibiotics and provides protection against bacterial and fungal infection. The WHO recommends (citing this article, among others) that all people living with HIV who have a CD4 count of below 350 cells/µl
or have been classified as clinical stage III or IV be provided with prophylactic co-trimoxazole. In settings with high HIV prevalence, high infant mortality, and limited health infrastructure WHO recommends that all HIV-positive individuals receive co-trimoxazole prophylactic treatment (WHO et al., 2013). The analysis included 8 cohort studies and 1 randomized trial. The effect co-trimoxazole had on mortality was seen if initiated before ART, with ART, or after the patient was stable on ART. There was no evidence of change in the benefit of co-trimoxazole after CD4 count gains following initiation of ART. Providing cotrimoxazole can also, “help increase the retention rate, provide an opportunity to assess an individual’s adherence to treatment before the start of ART, and improve survival in those not on ART,” (Suthar et al., 2012: 134). (Gray II) (treatment, co-trimoxazole, Cambodia, Ethiopia, Malawi, South Africa, Uganda, Zimbabwe)

• A study in Uganda and Zimbabwe using patients from the DART Trial found that co-trimoxazole prophylaxis improved survival in patients in the first 72 weeks on ART. A total of 3,179 adult patients (65% women) were observed between 2003 and 2008. All patients had CD4 counts under 200 cells. Ten percent did not take co-trimoxazole during the follow-up, 62% were taking co-trimoxazole at ART initiation and the remaining 28% started while on ART. Co-trimoxazole use in patients who started during or before ART initiation halved mortality in the first 12 weeks on ART. The overall mortality rate was reduced by 35%. Benefit did not vary with increasing time on co-trimoxazole. On the other hand, when time on ART initiation was considered, mortality reduction was the greatest in the first 12 weeks of treatment. The reduction in mortality was sustained from 12 to 72 weeks, but not evident after 72 weeks of ART initiation. Average 5 years survival increased by 5% and 2% in patients who started ART at CD4 count 15 or 150 cells, respectively. Use of co-trimoxazole started before or at initiation of ART reduced risk of deaths potentially preventable by co-trimoxazole (malaria, toxoplasmosis, cryptococcal meningitis, diarrhea, septicemia etc.) by 21%. After 72 weeks no difference in co-trimoxazole effect was observed. The study also found that use of co-trimoxazole was associated with 26% reduction in risk of new malaria episode (Walker et al., 2010). (Gray II) (treatment, co-trimoxazole, Uganda, Zimbabwe)

• Services in rural Uganda which provided participants living with regular three month follow up, including screening for ART eligibility plus provision of co-trimazloe prophylaxis found that between 2007 and 2008, of 322 patients who learned their HIV-positive serostatus any time between 2004 and 2008, 79.2% had been screened for ART. Of those eligible for ART, 99% had initiated ART. Prior to ART initiation, patients received three counseling sessions, a medical exam and identified a treatment supporter. On starting ART, patients were seen at 2 weeks, four weeks and then at 3-month intervals or more often if needed (Kazooba et al., 2012). (Gray IIIb) (treatment, counseling, Uganda)

• A study done in Kenya showed that provision of free co-trimoxazole in antiretroviral therapy-ineligible clients improved survival. A total of 5,175 clients had baseline CD4 counts among the 5,854 clients enrolled in to a clinic in Nairobi between 2005 and 2007. Fifty three percent (1,024) of the clients who had WHO stage 1 or 2 disease and CD4 counts above 250 were ineligible for ART. Sixty percent of clients accessed care before co-trimoxazole was routinely offered for free and the remaining 40% before free co-trimoxazole made available. Women represented more than 70% of the clients. The one year retention in care was 84% for ART-ineligible clients enrolled when free co-trimoxazole was available compared to 63% retention for clients who were enrolled in the period when co-trimoxazole was not routinely offered for free. Clients who were enrolled to care in the period when co-trimoxazole was not free were more than 2.5 times likely to be lost to follow-up and die. Results were similar for clients who had CD4 counts between 251 and 350 cells and above 350 cells (Kohl er et al., 2011). (Gray IIIb) (treatment, co-trimoxazole, Kenya)

• An observational cohort study conducted in South Africa showed that use of co-trimoxazole preventive therapy at initiation of antiretroviral therapy increased survival among HIV/AIDS patients. The use of co-trimoxazole prevented Pneumocystis jirovecii infection and toxoplasmosis. In resource limited countries, use of co-trimoxazole alleviated the burden of life threatening
infections such as malaria, bacterial pneumonia and diarrhea among HIV positive patients. In South Africa even though malaria and Pneumocystis jirovecii pneumonia are not as prevalent and cotrimoxazole resistance is high, cotrimoxazole therapy reduced mortality at any CD4 count on initiation of antiretroviral therapy. A total of 14,097 patients (38% women) were recruited from 231 clinics who started antiretroviral therapy between January 2003 and 2008. Cotrimoxazole preventive therapy was initiated for 53% of the patients and continued for a mean period of 9 months according to international and WHO recommendations. Reduced mortality was associated with higher CD4 count at initiation of antiretroviral therapy. Cotrimoxazole use was strongly associated with lower mortality, with a 36% decrease in mortality. On the other hand, cotrimoxazole prophylaxis was not associated with reduction in mortality among patients who had both higher CD4 count and stage 1 and 2 WHO clinical diseases at antiretroviral therapy initiation (Hoffmann et al., 2010b). (Gray IIIb) (treatment, co-trimoxazole, South Africa)

6. **Home- and community-based antiretroviral treatment may be effective, but attention must be paid to potential effects of stigma and discrimination.** [See also Strengthening the Enabling Environment]

- A randomized controlled trial was done in Uganda following patients on ART between 2005 and 2009 in groups that were treated with either a home-based care regimen or a routine clinic-based care system. Mortality rates were similar in both treatment groups, even among patients starting ART at CD4 counts of less than 50 cells/µl. In both clinic- and community-based care, those patients who initiated care at a CD4 count of less than 50 cells/µl had significantly higher mortality rates, and the rates for all participants were significantly higher in the first 6 months than they were in the subsequent follow-up period. Overall, 1,453 adult patients initiating ART between 2005 and 2006 were followed until 2009. Clusters were put together by geographic area and then randomized into either the home-based care group or the clinic-based care group. Patients were started on ART following Ugandan guidelines of initiation at CD4 counts at or below 200 cells/µl or late stage III or stage IV disease. About 71% of the patients were women, the median age was 37 years old, and 31% of patients had CD4 counts of less than 50 cells/µl at baseline. Routine clinic-based care involved patients picking up their medication and receiving adherence support monthly at the clinic. They also had clinical visits at 2 and 3 months, and then every 3 months thereafter. Home-based care involved patients receiving lay healthcare workers at their homes monthly. These healthcare workers would travel by motorbike to each home, would assess the patients clinically, deliver the ARVs, and provide adherence counselling. They had access to a phone so that they could contact the clinic if they had any questions. The healthcare workers could also refer patients to the clinic if necessary, and patients would attend the clinic for clinical visits at 2 and 6 months, and then every 6 months thereafter. Even when the patients attended clinic, they had a home visit that month to receive their ARVs. There was an overall mortality rate of 6.36 deaths per 100 person-years of follow-up. There was no statistically significant difference between the cohorts at either CD4 count level, but there was a significant difference between the mortality of those with a baseline CD4 count of less than 50 cells/µl and a baseline CD4 count of more than 50 cells/µl. In the first 6 months of treatment, the mortality rate for all participants was 16.5 deaths per 100 person-years, and in the remaining follow-up period the mortality rate was 3.52 deaths per 100 person-years. There was a significantly higher mortality rate in the first 6 months of ART regardless of treatment group. Among the patients who had a CD4 count of less than 50 cells/µl at baseline, there was a higher proportion of deaths attributable to tuberculosis in the home-based care cohort and a higher proportion of deaths attributable to poor nutritional intake in the clinic-based care cohort (Woold et al., 2014). (Gray II) (treatment, home-based care, Uganda)

- A randomized trial done in Uganda found similar survival rates, plasma viral suppression and reduced cost when patients on ART were followed at home versus at a health facility. A total of 859 patients (73% women) were randomized to home-based care and 594 patients (68% women) to facility-based care and followed between 2006 and 2009. Counseling and information were provided for each patient at the initiation of ART and drugs for one month were given with a pill
HIV testing with pre-uptake of ART. Eigh-teen percent of patients in home care and testing program that included point-of-care CD4 testing and facilitated referrals to HIV care. They carried mobile phones to facilitate referral when needed. All patients were invited to the clinic for routine reviews at 2 and 6 months after initiation of ART and every 6 months thereafter. In the health facility care group, patients were scheduled at 2 and 3 months after initiation of ART and every 3 months thereafter. Rate of mortality or virological failure (viral RNA above 500 copies) was 26% both in home (11.29 per 100 person-years) and facility (11.45 per 100 person-years) cared patients. Adherence to therapy in the past 28 days was 94% for home and 91% for facility cared patients. By the end of the study, 566 (66%) in the home and 377 (63%) patients in the facility group were alive and on follow-up with full viral suppression. Sixteen percent of patients in home care and 21% in facility care had a drug substitution at 8 months after initiation of ART. The total cost per patient per year was 793 US$ for home care and 838 US$ for facility care (Jaffar et al., 2009). (Gray II) (treatment, home-based care, Uganda)

- A prospective observational cohort study was conducted in Rwanda from 2007 to 2009 to compare the standard of care to a community-based program in addition to the standard of care. The study found that 85% of the community cohort and 79% of the standard of care cohort was retained in care with viral load suppression at 1 year. The community cohort had lower rates of death and loss to follow-up, and a higher probability of suppressed viral load at 1 year after multivariate analysis. A group of 610 patients were initiated according to national program guidelines at CD4 counts of less than 350 cells/µl and followed for at least a year. Standard of care included ART and cotrimoxazole provided monthly free of charge at the clinic. CD4 counts were taken every 6 months after initiation of care. Counseling was also provided. The community-based program included community health workers visiting patients in their homes every day. These health workers provided social support, monitored the health of their patients, and directly observed therapy once a day. The health worker also accompanied the patients to health visits for the first 4 monthly visits. A food ration was provided for the first 10 months of ART, and a transportation stipend was available for clinic visits. There was additional support provided to those in need, which included payment of school or insurance fees, microfinance loans, employment aid, and repairs in the household. There were 306 patients in the standard of care cohort and 304 patients in the community care cohort. Sixty-six percent of the patients in the standard of care were women, while 58% in the community cohort were women. The mortality rate in the standard of care cohort was 7.2% and 4.3% in the community cohort. A total of 3.3% of the standard of care cohort and 1% of the community cohort were lost to follow-up. Patients in community-based care had a 15% greater probably of being retained in care with suppression of viral load at 1 year. Both programs had high rates of retention to care, at 92% in the community cohort and 87% in the standard of care cohort (Franke et al., 2013). (Gray IIIa) (treatment, community-based care, Rwanda)

- A global review of 90 studies in lower and middle income countries found that community-based services were most cost-effective compared to facility based programs. The review found that an integrated continuum of care, with a formally established affiliation between facility based programs and community-based programs resulted in better HIV treatment patient outcomes with lower rates of loss to follow up. Facilities can provide ART, with community sites providing condoms, adherence counseling, psychosocial support and other care (Amanyiwe et al., 2014). (Gray IIIb) (treatment, community-based care)

- A study was conducted from 2011 to 2012 in South Africa to evaluate a home-based counseling and testing program that included point-of-care CD4 testing and facilitated referrals to HIV care. The home-based counseling and testing program achieved high rates of testing, linkage to care, and uptake of ART. Eighty-six percent of participants who were eligible initiated ART by 3 months. For participants with a CD4 count of less than 200 cells/µl, the proportion with viral suppression increased from 20% at baseline to 80% at 6 months. A questionnaire about demographics, sexual behavior, and history of HIV testing was conducted at the initial visit on 671 adults, along with a HIV testing with pre- and post-test counseling. Thirty percent of the participants were HIV-
positive; 36% of the HIV-positive individuals were newly identified. An additional questionnaire was administered to the HIV-positive participants, which included questions on sexual behavior, HIV testing and knowledge, HIV clinic visits, and ART initiation. These patients also received point-of-care CD4 testing to see if they were eligible for ART under South Africa’s initiation guidelines (CD4 below 200 cells/µl until August 2011, when it was changed to CD4 below 350 cells/µl). The counselors encouraged the participants who were eligible for treatment to visit their local clinic. Follow-up visits for the HIV-positive participants were conducted at 1, 3, and 6 months to assess ART initiation and to provide counseling on HIV care and adherence. The median age of HIV-positive participants was 34 years, 82% were female, and 30% were employed. Of the HIV-positive women, 52% did not know their partner’s status, and 22% reported having an HIV-positive or the probability of HIV-positive partner. Ninety-two percent of those who knew they were HIV-positive reported that they had a CD4 count previously done, but only 52% reported receiving their results. Only 57% of HIV-positive participants had visited an HIV clinic at baseline, while 96% had visited a clinic at 6 months. Reported condom use at last sexual encounter for HIV-infected participants increased from 44% at baseline to 68% at 6 months. Home-based counseling and testing with point-of-care CD4 testing and facilitated referrals improved rates of HIV testing, ART initiation, and viral suppression; however, there was one reported case of social harm where a participant lost their income and residence. In this case, they returned to live at home with support within 3 months (van Rooyen et al., 2013). (Gray IIIb) (treatment, home-based care, South Africa)

7. Integration of HIV and AIDS services into primary care increases access to testing and treatment services. [See Structuring Services to Meet Women’s Needs]

7A. Gaps in Programming—Treatment: Provision and Access

1. Barriers such as cost of medications, stigma, long clinic waits, lack of food, and child-care responsibilities may discourage women living with HIV from accessing antiretroviral therapy.
2. Initiatives that provide for early diagnosis and appropriate longitudinal care prior to treatment eligibility are needed to reduce mortality rates and costs among adults accessing treatment.
3. Adequate supply planning and secure funding are needed to avoid ARV stock-outs and use of obsolete medications.
4. Information systems need better data on distribution of services, effectiveness of services, and how well services are matched to populations and subpopulations in need of HIV treatment and care.
5. Interventions are needed to counter gender norms that discourage men from attending health services until they are extremely sick.
6. HIV surveillance systems do not count those over age fifty, particularly women, and treatment guidelines are missing for this age group.
7. Well-functioning laboratory systems are needed to measure viral load via PCR to assess effectiveness of treatment.
8. Interventions are needed to ensure that prisoners have ongoing access to HIV treatment and care.
9. Additional outreach programs are needed for patients who miss ART clinic visits or fail to initiate treatment.
10. Scale up of testing is needed with competent staff and labs in order to assess CD4 counts and link those who test HIV-positive to treatment.

11. Increased links are needed for women who access treatment to receive counseling concerning desired children and contraception.

12. Treatment programs need strategies to retain patients on treatment for countries affected by humanitarian emergencies (refugees of war, internally displaced people, etc.).

13. Improvements are needed in health services, such as increased or flexible clinic hours, to reduce wait times and to encourage ART initiation.

14. Treatment programs that meet the needs of key populations such as sex workers and trans populations are needed.

15. Improved support systems for lay or basic health workers are needed to facilitate effective care in areas where lay health care workers provide a significant proportion of HIV care.

16. Research is needed on treating anemia, malnutrition and other dietary conditions as well as on optimum micronutrients for patients accessing ART and for patients prior to accessing treatment.

17. Pregnant women living with HIV need timely access to CD4 count testing and results to access treatment.

18. Adolescents living with HIV need information and services through adolescent-friendly HIV and contraception services.

1. **Barriers such as cost of medications, stigma, long clinic waits, lack of food, and childcare responsibilities, among others, may discourage women living with HIV from accessing antiretroviral therapy.** A study found that patients who were living with HIV but did not access antiretroviral therapy were twice as likely as patients on antiretroviral therapy to report not having enough food to take with treatment as a concern, in addition to concerns about cost barriers. Another study found that cost of ARVs, with direct out of pocket payment at point of care delivery decreased access to ARVs. Another study found transport costs and waiting time a barrier to access to treatment. Increased efforts are needed so that those in pre-ART care understand that HIV can be transmitted prior to ART eligibility.

   - Gap noted, for example in **Zambia** (Fox et al., 2010a); **Burkina Faso** (Kouanda et al., 2010b); **India** (Thomas et al., 2009); **Mozambique** (Posse and Baltussen, 2009); **Uganda** (Geng et al., 2010b; Tuller et al., 2010; McGrath et al., 2012); **Zimbabwe** (Skovdal et al., 2011c); **Colombia** (Arrivillaga et al., 2009); **Tanzania** (Wringe et al., 2009 cited in Geng et al., 2010a); **Indonesia** (Riyarto et al., 2010); **Sub-Saharan Africa** (Mills et al., 2006); **South Africa** (Smith et al., 2013a); globally (WHO, 2013).

2. **Initiatives that provide for early diagnosis and appropriate longitudinal care prior to treatment eligibility are needed to reduce mortality rates and costs among adults accessing treatment.** A review found that early mortality among adults accessing antiretroviral therapy can be attributed to late diagnosis of HIV. Despite multiple interactions with parts of the healthcare system, a study of women in Uganda found that late presentation for HIV care resulted largely from the, “inability of the medical system to link women to appropriate care,” (McGrath et al., 2012: 1095). Women entered care only when symptomatic. Another study found that more than a quarter of HIV patients in care prior to ART initiation
did not start ART according to national guideline criteria. Another study found that women did not know where to go to access treatment. A review found that a process is needed to optimize transfers of care without treatment interruption and with appropriate medical documentation. Another study found that over half of patients who were not yet known to be eligible for ART at enrollment but who had tested HIV-positive, including a quarter who had CD4 counts taken, were lost to follow up. Another review found that asymptomatic patients perceived little need to initiate ART. Another study found that those with higher CD4 counts who were not yet eligible for ART lacked social support and social capital, yet needed this support.

- Gap noted, for example, in Sub-Saharan Africa (Lahuerta et al., 2013; Mugglin et al., 2012b; Kranzer et al., 2012; Lawn et al., 2008); resource-limited settings (Geng et al., 2010a); Malawi and Kenya (Zachariah et al., 2011b; MacPherson et al., 2012a); China (Zhou et al., 2011); Ethiopia (Alemayehu et al., 2009; Mulissa et al., 2010; Assefa et al., 2011); Vietnam (Nam et al., 2010); Uganda (McGrath et al., 2012; Wakeham et al., 2010; Miro et al., 2010); Mozambique (Auld et al., 2011; Lahuerta et al., 2012; Pati et al., 2013); Malawi (McGrath et al., 2010); Kenya (Taylor-Smith et al., 2011; Guthrie et al., 2011); West Africa (Lewden et al., 2012); East Africa (Mujugira et al., 2012); South Africa (Lessells et al., 2014; Smith et al., 2013a; Faal et al., 2011; Clouse et al., 2013; McGrath et al., 2013); Zambia (Scott et al., 2014); globally (WHO, 2013); Kenya, Mozambique, Rwanda and Tanzania (Lahuerta et al., 2014); global review of PEPFAR-funded countries (IOM, 2013).

3. Adequate supply planning and secure funding are needed to avoid ARV stock-outs and use of obsolete medications. “As ART cannot be interrupted without risk of development of drug resistance – and hence worse survival – people on ART need an uninterrupted supply…” (WHO, 2014a: 32). The Coordinated Procurement Planning Initiative, which monitors the supply of ARVs in 22 countries, found that at any point half of these countries were at high risk of stock out (WHO, 2014a). Between 30% and 45% of low- and middle-income countries have annually reported stock outs in recent years (WHO, 2014a). Studies in multiple sub-Saharan African countries report stock shortages and stock outs as major risk factors for treatment interruption. “….Models of supply chain management need to be directly tied to health outcomes to ensure that the priority is improving health rather then reducing costs” (Ying et al., 2014, para 17).

• Gap noted globally in lower- and middle-income countries (WHO, 2014a; Ying et al., 2014) Côte d’Ivoire (Pasquet et al., 2010 cited in Kranzer and Ford, 2011); Cameroon (Marcellin et al., 2008 cited in Kranzer and Ford, 2011); globally in PEPFAR-supported countries (IOM, 2013); Malawi and Uganda (Hsieh, 2013).

4. Information systems need better data on distribution of services, effectiveness of services, and how well services are matched to populations and subpopulations in need of HIV treatment and care. A review of PEPFAR data plus site visits to 13 PEPFAR partner countries plus 400 interviews found a lack of data on distribution of services and effectiveness of services for treatment of people living with HIV.

• Gap noted globally (IOM, 2013).

5. Interventions are needed to counter gender norms that discourage men from attending health services until they are extremely sick. Studies have shown that norms of masculinity prevent men from accessing ART until severely symptomatic.
• Gap noted globally (IOM, 2013); and for example, in Africa (Druyts et al., 2013); Zimbabwe (Takarinda et al., 2015; Skovdal et al., 2011b); Uganda (Kanters et al., 2013; Siu et al., 2012; Siu et al., 2013); Zambia (Gari et al., 2014; Musheke et al., 2013a); Tanzania (Nyamhanga et al., 2013).

6. **HIV surveillance systems do not count those over age fifty, particularly women, and treatment guidelines are missing for this age group.** Currently, 4.2 million people live with HIV globally with increasing numbers of people over the age of 50 living with HIV. Few studies assess prevalence among women above age 50. Integration of treatments for common chronic diseases of old age will need to be integrated into HIV services.

• Gap noted globally (UNAIDS, 2014a; Salamander Trust, 2014; Mills et al., 2012a); in Africa (Bendavid et al., 2012b; Negin et al., 2012); Zimbabwe (Negin et al., 2014 cited in Mahy et al., 2014).

7. **Well-functioning laboratory systems are needed to measure viral load via PCR to assess effectiveness of treatment.** However, adequate clinical results can also be cost-effective and meet patient needs. A study in sub-Saharan Africa found that more than half of test results for viral load were invalid or inaccurate. A review done in low and middle-income countries showed that lack of routine virologic monitoring in resource limited ART programs led to the development of cross-resistance to the NRTI component of second-line treatment. Even where virological monitoring is available and demonstrates virological failure, delayed switching of patients to alternative antiretroviral therapy regimens occurs.

• Gap noted, for example, in globally in resource-limited settings (Phillips et al., 2011; Sawe and McIntyre, 2009); Sub-Saharan Africa and Africa (Greig et al., 2011; Ford et al., 2009b); India, Cameroon, Kenya, Malawi, Burkina Faso, South Africa, Nigeria and Senegal (Luca et al., 2010); Honduras (Murillo et al., 2010).

8. **Interventions are needed to ensure that prisoners have ongoing access to HIV treatment and care.** Studies found that prisoners lacked access to ARVs, or for those who accessed ARVs, faced the dangers of interrupted treatment due to prison transfers.

• Gap noted, for example, in globally (Jurgens et al., 2007); Namibia (Legal Assistance Center AIDS Law Unit and University of Wyoming College of Law, 2008).

9. **Additional outreach programs are needed for patients who miss ART clinic visits or fail to initiate treatment.** A study showed that issues such as provider to patient ratios; adherence support programs; and needing transport from rural areas were associated with lower CD4 counts at initiation of ART. Other studies showed that patients were lost between initiation and maintenance sites. Another study found that one in five treatment-eligible HIV-positive individuals refused to initiate ART (Katz et al., 2011). Others who dropped out of treatment were using unproven remedies.

• Gap noted, for example in Ethiopia, Kenya, Lesotho, Mozambique, Nigeria, Rwanda, South Africa and Tanzania (Nash et al., 2011); Zambia (Musheke et al., 2013b); South Africa (Katz et al., 2011; O’Conner et al., 2011; Bassett et al., 2010; Cornell et al., 2010); Botswana (Steele et al., 2011); Uganda (Nakigozi et al., 2011; Geng et al., 2012b, abstract); Latin America and the Caribbean (Crabtree-Ramirez et al., 2011).

10. **Scale up of testing is needed with competent staff and labs in order to assess CD4 counts and link those who test HIV-positive to treatment.** Studies are finding that in some
countries, those who test HIV-positive are presenting with AIDS and that patients do not initiate ART despite eligibility. Those who test HIV-positive yet not eligible to receive antiretroviral therapy according to their national guidelines often did not remain in care until they were eligible for treatment.

- Gap noted, for example, in Rwanda (Kayigamba et al., 2012); Uganda (Miiro et al., 2010; Chami et al., 2012, Abstract); South Africa (Lessells et al., 2011; Losina et al., 2010; Kranzer et al., 2010; Larson et al., 2010); China (Sullivan et al., 2010b); Ethiopia, Kenya, Malawi, Mozambique, and South Africa (Rosen and Fox, 2011); South Africa (Naughton et al., 2011); Ethiopia (Assefa et al., 2010).

11. Increased links are needed for women who access treatment to receive counseling concerning desired children and contraception. [See also Meeting the Sexual and Reproductive Health Needs of Women Living with HIV and Safe Motherhood and the Prevention of Vertical Transmission] A study with patients from multiple sites in sub-Saharan Africa found that within four years of follow up for 4,531 women, one-third experienced a pregnancy.

- Gap noted, for example, in Sub-Saharan Africa (Myer et al., 2010).

12. Treatment programs need strategies to retain patients on treatment for countries affected by humanitarian emergencies (refugees of war, internally displaced people, etc.). Researchers found that patients faced challenges accessing treatment and continuing to stay on ARVs with floods, political crises and strikes.

- Gap noted in Mozambique, South Africa and Zimbabwe (Veenstra et al., 2010).

13. Improvements are needed in health services, such as increased or flexible clinic hours, to reduce wait times and to encourage ART initiation. Interviews with people living with HIV eligible for ART who refused ART found that “the problem is…services…The process is so long” (Musheke et al., 2013a: 236). In addition, waiting to access ART jeopardizes livelihoods. Information systems that can track patients across sites can assist in tracking patients who need care.

- Gap noted, for example, in Zambia (Musheke et al., 2012; Musheke et al., 2013a); Sub-Saharan Africa (Lahuerta et al., 2013); Malawi (MacPherson et al., 2012b); Vietnam (Nguyen et al., 2013).

14. Treatment programs that meet the needs of key populations such as sex workers and trans populations are needed. Recent WHO guidelines (WHO, 2014b) have noted that key populations living with HIV should have the same access to ART and ART management as other populations.

- Gap noted, for example, in Dominican Republic (Donastorg et al., 2014); Latin America and the Caribbean (PAHO et al., 2014).

15. Improved support systems for lay or basic health workers are needed to facilitate effective care in areas where lay health care workers provide a significant proportion of HIV care. Systems need to be developed specifically for remuneration, retention, and adequate supervision.
• Gap noted, for example, in **Botswana** (Ledikwe et al., 2013 cited in Bemelmans et al., 2014); **Sub-Saharan Africa** (Mwai et al., 2013 cited in Bemelmans et al., 2014); **Mozambique** (Rasschaert et al., 2014 cited in Bemelmans et al., 2014).

16. **Research is needed on treating anemia, malnutrition and other dietary conditions as well as on optimum micronutrients for patients accessing ART and for patients prior to accessing treatment.** [See Care and Support: Women and Girls]

17. **Pregnant women living with HIV need timely access to CD4 count testing and results to access treatment.** [See Safe Motherhood and Prevention of Vertical Transmission: Antenatal Care-Treatment]

18. **Adolescents living with HIV need information and services through adolescent-friendly HIV and contraception services.** [See Prevention for Young People: Increasing Access to Services]

• Gap noted for **South Africa** (Evans et al., 2013).
7B. Treatment: Adherence and Support

Treatment adherence is necessary to continually suppress the virus. Adherence to ART leads to better virological outcomes, prevents disease progression and improves survival (Nachega et al., 2010a; Nachega et al., 2010c). Conversely, inadequate adherence leads to drug resistance, which can then be transmitted to others (Simon et al., 2010) and lead to disease progression and death (Nachega et al., 2010c). “Preventing adherence-related treatment failure is especially important in resource-limited settings wherein second-line therapy is up to 17 times more expensive than first line therapy and often unavailable” (MSF, 2010 cited in Pop-Eleches et al., 2011: 831). WHO 2013 guidelines also note that the first ART regimen offers the best opportunity for effective virologic suppression and requires that medication be taken exactly as prescribed (WHO, 2013: 89). Simple, safer, once-daily, single-pills for first line therapy are now the standard of care (WHO, 2013) and multiple pill regimens for first line therapy are being phased out.

Treatment has been successfully administered with good adherence in many populations and groups, including among sex workers (Huet et al., 2011: para 21); and people who inject drugs (Werb et al., 2010; Malta et al., 2010; Wisaksana et al., 2010; Wood et al., 2008; Mimiaga et al., 2010). However, while HIV prevalence globally among female sex workers is 12% (36.9% in Sub-Saharan Africa) (Baral et al., 2012), ART use among female sex workers living with HIV is only 38% (Mountain et al., 2014). Female sex workers are 12 times more likely to be living with HIV than women in the general population (UNAIDS, 2014a). More studies are needed to elucidate and overcome barriers to treatment and adherence for sex workers, such as discrimination by providers (Mountain et al., 2014). [See also Prevention for Key Affected Populations] Studies in Canada and France among people who use drugs found that those who were prescribed opioid agonist therapy had higher rates of adherence to antiretroviral therapy and longer-term virological success (Uhlmann et al., 2010; Roux et al., 2009). [For information on interactions between antiretrovirals and opioid agonist therapy, please refer to Bruce et al., 2010 and Altice et al., 2010: 68-69.]

Continuous Monitoring is Needed to Ensure Viral Suppression

HIV care and treatment programs have largely been evaluated by the numbers enrolled in care (McNairy and El-Sadr, 2012). Monitoring adherence requires multiple approaches including viral load monitoring, pill counts and measurements and self-reports, among others. In 2013, the World Health Organization recommended the use of routine viral load measurement as the preferred way of monitoring treatment outcomes (WHO, 2013) beyond merely counting the number of people started on ART (Collins, 2014). Also in 2013, UNAIDS launched the 90/90/90 global treatment campaign that, in addition to 90% of people living with HIV knowing their status and 90% of all people diagnosed with HIV receiving sustained ART, envisions that 90% of all people receiving ART will have viral suppression by 2020 (UNAIDS, 2014b). While these goals may be ambitious, some countries are on course to

—I’m 18 years, you are telling me drugs for life?—
—Woman living with HIV in Uganda (Hsieh, 2013: 11)
achieve the viral suppression target: in a nationally representative survey, 82.3% of patients on ART in Rwanda were found to be virologically suppressed (Binagwaho et al., 2014). New HIV infections in Rwanda fell 60.3% and AIDS-related mortality dropped 82.1% between 2000 and 2012, which may be a result of high rates of virological suppression among those living with HIV (Binagwaho et al., 2014). But there is still a long way to go: UNAIDS estimates that in sub-Saharan Africa, only 29% of people living with HIV are virally suppressed (UNAIDS, 2014b).

A study in Canada with 1,305 patients confirmed that once viral suppression was initially achieved, adherence of at least 95% or greater was needed to maintain viral suppression: after adjusting for duration of suppression, individuals with adherence less than 95% were 11% more likely to rebound, i.e., experience an HIV viral load increase, than those who were adherent 95% or more of the time (Lima et al., 2010). However, the adherence requirement of over 95% is based on the use of unboosted protease inhibitors (PI), which are less available in resource-limited settings (Chung et al., 2011). In resource-limited settings, most antiretroviral regimens contain non-nucleoside reverse transcriptase inhibitors (NNRTI), such as nevirapine or efavirenz, which have long half-lives and may remain in the patient’s body for weeks. Thus, antiretroviral resistance may not occur in patients on NNRTI regimens until their adherence drops below 80% (Cressey et al., 2005 cited in Chung et al., 2011). Still, treatment adherence remains critical to viral suppression and improved survival.

**Addressing Barriers to Treatment Adherence is Critical to Maintaining High Levels of Retention**

Improved reporting is needed to assess why people discontinue therapy and how to keep patients adherent to antiretroviral therapy (WHO et al., 2011b). A systematic review of 84 studies examining barriers to treatment adherence found “fear of disclosure, forgetfulness, a lack of understanding of treatment benefits, complicated regimens, and being away from medications were consistent barriers to adherence in developed and developing nations. More common to developing country settings were issues of access, including financial constraints and a disruption in access to medications” (Mills et al., 2006: 18). Clearly, when patients have to pay for ARVs in resource-limited settings in a context of poverty, access and adherence will be negatively affected (Lal et al., 2010; Ruanjahn et al., 2010). Having to walk long distances to access services is another factor – in one study in Zambia, over half of patients had to walk for more than one hour to access services (Sasaki et al., 2012). WHO reports that of 118 countries reporting, 38% reported at least one or more ARV stock outs in health facilities during 2009 (WHO, 2010 cited in Atun and Bataringaya, 2011; WHO et al., 2011b), which can make adherence unachievable for

“I feared my husband would know, and if he knew, he was going to divorce me. Where can I go if I get divorced? Who will look after my children? I just said to myself that it is better that I stop medication so that I can protect my marriage, and so that my children can have a future.”

— Woman living with HIV who stopped treatment, Zambia (Musheke et al., 2012: 4)
patients. To address the issue of stock-outs, WHO has developed key indicators to monitor the performance of supply chain management systems (WHO, 2011e).

In 2009, 18% of people who started antiretroviral therapy in low- and middle-income countries were no longer in care within 12 months (UNAIDS, 2011a). Average retention at 12 months after initiating antiretroviral therapy was 67% at 60 months, with 46 countries reporting (WHO et al., 2011b). Globally, retention at 12 months is similar among women and men (WHO et al., 2011b). In a recent study of 4,147 patients in 17 facilities in Tanzania, Uganda and Zambia, retention ranges from 25.8% to 90.4% at year four (Koole et al., 2014), showing that some sites are in need of critical improvements to improve retention to care. Additional research is needed to understand why adherence interventions are effective in some settings yet not effective in other settings (Chaiyachati et al., 2014).

**There Are Gender Differences in Treatment Adherence**

For the most part, men and women have similar adherence rates, though a few studies have found higher rates of non-adherence in women (Puskas et al., 2011). There are, however, gender differences in predictors of adherence. Women may need family support, including redistribution of household responsibilities, to enable them to adhere to treatment. Even if drugs are free or subsidized, women may not be able to afford the time or money required to travel to a clinic. A qualitative study of women living with HIV in Colombia found that women prioritized the needs of their HIV-positive children over their own adherence needs (Arrivillaga et al., 2011). Women in Malawi and Uganda also reported challenges in managing their own adherence as well as that of their children (Hsieh, 2013). Some women sold their ARVs to survive financially (Arrivillaga et al., 2011). Women may also have difficulty navigating treatment when it conflicts with other activities for survival. Sex workers, in particular, face difficulties in adherence in large part due to stigma and discrimination. [See Strengthening the Enabling Environment & Prevention Among Key Affected Populations: Female Sex Workers] One South African sex worker points out the struggles she faces: “If you don’t pay off the police, they take you to jail…you can’t take antiretroviral drugs or any medication you need” (Arnott and Crago, 2009: 10). Women sex workers in Vietnam reported that they were not allowed to join networks of people living with HIV who gained access to valuable support and information services because they were seen as “social evils” rather than “innocent wives getting the disease from their husband” (Nguyen et al., 2013: 218).

Side effects can also deter women from adhering to treatment plans. Some medications cause a redistribution of body fat resulting, for example, in a large belly, or a collection of fat at the base of the neck, or loss of fat from the cheeks (Mbonye et al., 2013; Han et al., 2011; Elliott et al., 2011). Women reported problems with adherence due to how ARVs changed their appearance with bodily changes creating visibility of their HIV-positive serostatus and

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“When I disclosed to my husband, He refused to accept. Whenever he finds my ARVs, he throws them in the latrine”

—Woman living with HIV who is a member of Women Fighting AIDS, Kenya (Machera, 2009: 19)
consequent stigma. Women may also be more adversely affected by the common side effects of ARVs that result in anemia. Yet a food assistance program in Mozambique did not increase adherence compared to those with no food assistance (Posse et al., 2013). A study of quality of life among people living with HIV in Cuba found that women reported higher levels of pain compared to men, and that pain interfered more in women’s lives than in men’s lives, and that overall, women did not enjoy the same health-related quality of life as men (Aragones-Lopez et al., 2012). In some countries, such as Vietnam, men (1,016 patients, 63.8% male) reported better quality of life on antiretroviral therapy than did women, as women cared for their husbands, some of whom injected drugs (Tran, 2012).

However, it is also clear that men face particular challenges in accessing and adhering to HIV treatment, as men’s ideal sense of masculinity may be threatened by disclosing their status and seeking treatment. Being physically strong, capable of hard work and having children were also seen as signs of masculine identity, which were threatened by being labeled HIV-positive. Furthermore, men often perceive health services as spaces for women and children rather than for them. Services can seem “male-unfriendly” (Skovdal et al., 2011d: 2). A study from South Africa found that men’s adherence was challenged by factors related to an enabling environment, such as conditions of employment, with problems getting time away from work for clinic visits or loss of income due to waiting in lines at clinics (Maskew et al., 2013).

Support groups and counseling for men may also be beneficial (Hsieh, 2013). Focus group discussions with men living with HIV on treatment who had disclosed to their partners in South Africa found that men wanted to access male-only support groups at clinics where they collect their medication with guarantees that their HIV status would not be disclosed outside of the support group setting. Despite the fact that support groups were available four times per week, men did not know of these support groups (Madiba and Canti-Sigaqa, 2012). Yet in a study in Uganda, men who were recipients of support, such as expenses for children’s education, or given livelihood options, such as goats, were more adherent than men without this support. Treatment may be undertaken by some men to regain health, self-worth, ability to work and provide for their families as a sign of their masculinity (Siu et al., 2012; Siu et al., 2013).

\textbf{Nondisclosure Contributes to Adherence Difficulties}

Disclosure can have both negative and positive consequences. Disclosure has the potential to lead to much needed support or it may lead to stigma, discrimination, abandonment or violence (Sasaki et al., 2012; Amanyeiwe et al., 2014). A study in Uganda found that internalized stigma was correlated with lack of disclosure, and suggested that stigma reduction efforts are key to increasing disclosure (Tsai et al., 2013). \textit{[See also Strengthening the Enabling Environment: Reducing Stigma and Discrimination]} A global review of stigma and adherence found that in some studies, disclosure was correlated with increased adherence, while in other studies, disclosure did not result in increased adherence. Where stigma was

\begin{quote}
\textit{"It involves being shouted upon like a child, don’t you see, no respect at all.”}

---Ugandan man reporting being scolded by nurses (Siu et al., 2013: 49)
\end{quote}
great, treatment was interrupted in order to conceal an HIV-positive status (Katz et al., 2013). A study in Botswana found that nondisclosure of positive HIV-status to a sexual partner was predictive of poor adherence rates (Do et al., 2010).

A woman may not disclose her status to her husband for fear of violence. A global survey of 2,035 adults living with HIV found that 17% of patients in long-term relationships had not disclosed their serostatus to their sexual partner. Patients feared the impact of disclosure on their relationships and their employment (Nachega et al., 2012). Studies of interventions to facilitate disclosure are lacking (Reda and Biadgilign, 2012). In some studies, men living with HIV reported caregiving and support from their sexual partner, however, women reported that disclosure resulted in a narrative of “neglect and violence (at times in life-and-death terms), often culminating in estrangement or divorce after the disclosure of their HIV-positive status to their male partners” (Schneider et al., 2012: 823). Some women in Uganda and Malawi feared violence or being ejected from their homes if they disclosed their positive serostatus (Hsieh, 2013; Omunakwe et al., 2014; Katz et al., 2013). [See also Strengthening the Enabling Environment: Transforming Gender Norms and Addressing Violence Against Women]

**Improving Treatment Adherence Requires Counseling, Empowerment to Overcome Barriers and Reduce Loss to Follow Up**

“I lost my marriage when I told my husband my status…so I did not tell my boss...Instead, I decided to stop going to the clinic so that she does not know my status.”

— Woman living with HIV who stopped treatment, Zambia (Musheke et al., 2012: 5)

“It is difficult for me to go to the doctor. I have to ask permission to leave work. This is not easy because if told (my bosses) that I have AIDS, they would fire me.... Nobody ever offers to take care of the kids.”

— Woman living with HIV in Colombia (Arrivillaga et al., 2011: 180).
Treatment programs must assess who gains access to treatment, how, and if it is accompanied by care and support. Does the program address adherence? Do patients receive adherence support? Do patients receive good quality counseling? Are patients satisfied with their quality of care? Have patients received proper information on medications and dosage? (Gruskin et al., 2007a). Programs should also promote treatment literacy so that all people know that AIDS cannot be cured but that ARV treatment can prolong life, with improved quality of life (IOM, 2013). For those on ARV therapy, treatment literacy is vital to understanding the importance of adherence. A survey in Togo found that patients who had good knowledge of the number of tablets per dose, the name of daily intakes and the times of drug intake had better adherence (Potchoo et al., 2010). Another survey in Cuba found that motivation was key (Beng et al., 2011).

Adherence may be best improved by addressing multiple levels simultaneously: with health providers that support families living with HIV, as well as community wide stigma reduction efforts (Katz et al., 2013). Ensuring that people are not lost to follow up is critical for maintaining treatment adherence. In some studies, men were more likely to be lost to follow up once on ART (Charurat et al., 2010; Tweya et al., 2010).

While there is little data demonstrating what works specifically for women in improving treatment adherence, there are some interventions that have been shown to work for both men and women such as provision of counseling, treatment support and treatment literacy. Counseling support by HIV-positive peers has been found to also be effective in improving treatment adherence in Thailand, through a model developed by the Thai Network of People With HIV/AIDS (TNP+). In Haiti, Rwanda and Lesotho, the Partners in Health’s “accompaniment” model, which includes daily home visits by community health workers, free clinic visits, nutritional support, transportation to clinics and preferential hiring of people living with HIV has also been found effective (Ford et al., 2009a). [See also Strengthening the Enabling Environment: Promoting Women’s Leadership] A study of MSM in the United States found when sexual partners regard themselves as a collective unit, those partners living with HIV had higher rates of viral suppression, suggesting that incorporating relationship dynamics into counseling is important (Gamarel et al., 2014). For migrant workers, mobile HIV services with longer lasting supplies of ARVs is a promising model for the many migrant populations who need reliable HIV treatment supplies (Lynch et al., 2012).

WHO recommends a combination of programmatic and individual level interventions to support adherence. Programmatic interventions to adherence include use of fixed dose treatment regimens, minimizing costs related to ART and ensuring commodity security. Individual level interventions include use of mobile phone reminders (Lester et al., 2010), peer support mechanisms such as support groups, nutrition support and management of mental health conditions and drug abuse (WHO, 2013).

The World Health Organization also provides guidance on decentralization of treatment and task shifting that may increase access to ART and impact both retention and adherence to
ART (WHO, 2013). Some progress is being made on decentralization: in 23 countries where Médecins sans Frontières is working, ART has been made available at more than 40% of public facilities in four countries and more than 20% in more than eight countries, while 13 out of 16 countries now allow lay counselors to provide ART adherence counseling (Lynch et al., 2012). Additional strategies such as the use of health workers to monitor adherence, task shifting and paid patient advocates (Igumbor et al., 2011; Braitstein et al., 2012) have all shown to increase adherence but are outside the scope of this compendium.

New technologies to facilitate adherence are also being developed (Haberer et al., 2010) such as the use of hand-held personal digital assistants to track and assess patients (Selke et al., 2010), lab results linked to mobile phone technology and connecting peers in an area. Physicians are poor predictors of whether a patient will be adherent (Walshe et al., 2010) and pill counts, viral load, and other externally validated ways should be used to measure adherence. These practices and tools are useful for both men and women. Although most adherence interventions address both men and women, further research is needed regarding the best ways to overcome a number of treatment adherence barriers specific to women such as fear of disclosure, stigma, violence, body image issues related to medication side effects, among others.

7B. What Works—Treatment: Adherence and Support

1. Adults in resource-poor settings, including key populations such as sex workers, have achieved good adherence to antiretroviral therapy with results similar to those achieved in resource-rich countries.

2. Fixed dose once-daily ARVs can improve adherence and clinical outcomes.

3. Peer support groups can increase adherence.

4. Counseling improves adherence.

5. Providing treatment support and literacy, including by HIV-positive peers and by providers, can increase adherence.

6. Pill counts and pillbox organizers increase adherence and are a low-technology empowerment tool.

7. Mobile phone text messages from health providers may improve adherence by providing patient support.

8. Community-based antiretroviral therapy programs may be as effective for adherence as facility-based programs, with lower costs for both patients and services.

9. Decentralization and integration of HIV services may increase adherence and early access to ART.

“These pills mean life to me, so if they were no longer accessible I would die.”
— Patient (Gilbert and Walker, 2009: 1126)
Promising

10. Frequent viral load monitoring can result in better health outcomes, including improved adherence and early identification of drug resistance.

11. Early active follow up when patients miss appointments may increase adherence.

B. Evidence

1. Adults in resource-poor settings, including key populations such as sex workers, have achieved good adherence to antiretroviral therapy with results similar to those achieved in resource-rich countries. [See also Treatment: Provision and Access]

   • A review of nine articles and 18 abstracts until 2006 from Sub-Saharan Africa, with 12,116 patients found favorable levels of adherence, with 77% of patients achieving 95% adherence according to patient self-reports. Adherence from studies in sub-Saharan Africa showed that that more patients were adherent than patients in North America, based on 31 studies with 17,537 patients (Mills et al., 2006). (Gray II) (treatment, adherence, Sub-Saharan Africa)

   • A systematic review and meta-analysis of 39 studies from female sex worker populations in Benin, Burkina Faso, Kenya, Rwanda, Zimbabwe, Canada, United States, India, Russia, Thailand, Vietnam, Dominican Republic, El Salvador, Brazil found that sex workers can achieve high rates of adherence. From 9 studies from Africa, Central America, the Caribbean and North America, 76% were adherent to more than 95% of prescribed pills. The pooled estimate of adherence for studies from LMIC was 76%. Similar to women in the general population, 57% on ART were virally suppressed, with study populations in Asia, Africa and Latin America. Three studies from Canada, USA and Dominican Republic found treatment experienced female sex workers who were no longer on ART. Loss to follow-up after ART initiation based on six studies from Kenya and Burkina Faso was 6%. Death following ART initiation based on six studies from Kenya and Burkina Faso was 6%. Female sex workers were defined as women who reported sex work within the previous six months or currently. Of the 39 studies included, 24 were prospective cohort studies, 12 were cross-sectional and 2 were retrospective case control. Median gains in CD4 count after 6 to 36 months ranged between 103 and 241 cells. However, current ART use among female sex workers was only 38%, with ever ART use greater among sex workers in high-income countries compared to LMIC (Mountain et al., 2014). (Gray IIIa) (treatment, adherence, Benin, Burkina Faso, Kenya, Rwanda, Zimbabwe, Canada, United States, India, Russia, Thailand, Vietnam, Dominican Republic, El Salvador, Brazil)

   • A retrospective observational study of 79 patients (84.2% men) who accessed ART at a private clinic in Argentina and were on ART for a median of 14 years found that 87.3% had an undetectable viral load. More than 90% had a median CD4 count of 516 (Socias et al., 2013). (Gray IIIb) (treatment, adherence, Argentina)

   • A prospective cohort study of 354 Rwandan women living with HIV on ART found that all reported complete adherence in the three days prior to their clinic visit, supported by changes in lab measures. The median CD4 count within six months prior to ART was 185 compared to 264 at the post-ART visit, which occurred nine to fifteen months following ART initiation. In addition, 94% refilled their medication at the appropriate time. In Rwanda, in order for a patient to become eligible for ARVs, they must attend a two to three day treatment literacy session, accept to be visited by a health care worker, have a fixed residence in a known catchment area of a health facility and disclose HIV status to a trusted family member, along with someone who will help
them with adherence. Adherence is reinforced at the community level by community health workers and/or a member of an association of people living with HIV. In addition, 96% of Rwandans have health insurance and ARVs are provided at no cost. Care was provided by an NGO with outreach efforts that included patient home visits (Musiime et al., 2011). (Gray IIIb) (treatment, adherence, Rwanda)

- A study in Botswana of 300 adult patients initiated in 2005 and found that 81.3% of patients were adherent based on four day and one-month patient recall and also based on clinic attendance for ARV medication refills during the prior three months. Adherence was defined as self-report of no missed ARV medication doses in the past four days; self-report of no missed ARV medication doses during the past one-month; and self-report of no missed ARV medication refill visits during the past three months. Adults receiving combination ART for one to six months had adherence rates of 77% and those receiving combination ART for more than twelve months had adherence rates of 79% (Do et al., 2010). (Gray IIIb) (treatment, adherence, Botswana)

- A cross-sectional study with quantitative and qualitative methods in 2007 with 422 patients in Ethiopia found an adherence rate of 88.1% based on unannounced pill counts (Beyene et al., 2009). (Gray IIIb) (treatment, adherence, Ethiopia)

2. Fixed dose once-daily ARVs can improve adherence and clinical outcomes.

- A meta-analysis of 19 randomized controlled trials was completed to investigate how pill burden and once-daily and twice-daily regimens of ART influenced adherence and virological outcomes. Higher pill burden was associated with reduced adherence and reduced rates of virological suppression, for both once-daily and twice-daily ART regimens. Adherence rates were higher in the once-daily ART regimens as compared to the twice-daily regimens. There was no statistically significant relationship found between virological suppression and once- or twice-daily ART regimen. Adherence and viral suppression decreased with longer follow-up time, but adherence decreased less with once-daily regimens than with twice-daily regimens of ART. The studies were published between 2004 and 2011 and were located primarily in high-income countries, with some data from middle- and lower-income countries. The trials included data from 6,312 individuals living with HIV. Adherence was measured with either pill counts or with medication event monitoring system caps. Adherence was 2.55% higher among participants following once-daily regimens as compared to patients following twice-daily regimens. There was no significant difference in treatment outcomes as measured by virological suppression between once- and twice-daily regimens of ART, which may be due to the minimal difference in adherence not translating to statistically significant outcomes. Decreasing pill burden in this meta-analysis was associated with better adherence and virological suppression, and adherence was improved with once-daily regimens as compared to twice-daily regimens (Nachega et al., 2014). (Gray I) (treatment, adherence)

- A meta-analysis of randomized controlled trials and cohort studies was done to compare the effect of fixed-dose combination ART and separate tablet regimens on adherence, virological suppression, and patient preference. The analysis demonstrated that fixed-dose combinations were associated with better adherence and to a lesser extent, increased virological suppression as compared to those not receiving fixed-dose ART. All studies reporting on patient preference indicated that patients preferred the fixed-dose combinations. The analysis included studies on partial fixed-dose combinations (where two pills were combined) and full fixed-dose combinations (where there was a single tablet regimen), as compared to regimens with a greater number of pills. Twenty-two papers, including data on 27,230 people, were included in the analysis. There were 6 randomized controlled trials, 10 prospective cohort studies, and 5 retrospective cohort studies. The studies were published from 1999 to 2013 and most were carried out in high-income settings. In most of the studies, less than half of the participants were women. The meta-analysis for viral suppression
which included 6 of the studies demonstrated greater virological suppression among patients on fixed-dose combinations. The analysis for adherence which included 5 of the randomized controlled trials indicated better adherence among the group on fixed-dose combinations. In the 4 studies that reported on quality of life, all reported better patient scores on fixed-dose combinations compared to separate pill regimens, including through quality of life score, a depression score, and self-perceived psychological fatigue. In one study, 97% of patients on fixed-dose combination treatment perceived their regimen to be ‘very easy’, compared to 81% of patients not on fixed-dose combination treatment. The authors of this meta-analysis write in favor of fixed-dose combinations that, “unlike other adherence support interventions which themselves require a degree of adherence, [fixed-dose combinations] require no further action on the part of the patient or provider as the intervention is an indivisible characteristic of the treatment,” (Ramjan et al., 2014: 510). (Gray I) (treatment, adherence)

- A global review of numerous randomized controlled trials found that once daily regimens improved adherence (Thompson et al., 2012; Ford et al., 2013b). (Gray I) (treatment, adherence)

3. **Peer support groups can increase adherence.**

- A randomized controlled trial with 68 women during a six-month period in rural India found that support by village women who received training resulted in statistically significant increased adherence. These village women received a three-day training to learn the basics of HIV/AIDS progression; the importance of adherence; coping strategies; the importance of nutrition; and life skills options. Supervision was ongoing. Women in the intervention group received six classes from the trained women on how to overcome barriers to adherence; how to reduce stigma; cooking tips for good nutrition; the benefits of earning income; and received a monthly supply of 2 kilos of food to cook. The women trained to provide support visited 5 women every week and worked to mitigate any barriers to adherence, such as providing bus fare for women to get to health services and accompanying the women to health services. The usual care group just received the six classes and chickpeas to cook. Adherence was measured by pill counts (Nyamathi et al., 2012). (Gray II) (treatment, adherence, support, India)

- A randomized trial of 48 women living with HIV in Nigeria who completed a six month follow up assessment found that motivational group support resulted in significantly higher levels of self-reported adherence. Among the intervention group, 93% reported never missing any medication compared to 40% of the standard of care group. Facilitators received a 24-hour training. Group support focused on topics such as discrepancies between current adherence behaviors and future goals (Holstad et al., 2012). (Gray II) (treatment, adherence, counseling, support, Nigeria)

- A cohort study conducted from 2007 to 2011 in South Africa followed participants in adherence clubs to study the effectiveness of group-based care led by non-clinical staff to prevent loss to follow-up, death, and virologic rebound. This data was compared to patients receiving routine care. Participation in an adherence club reduced loss-to-care by 57% and reduced virologic rebound by 67%. Ninety-seven percent of club participants remained in care at the end of the study as compared to 85% of patients in routine care. Participation was offered to adult patients who had been on ART for at least 18 months and had a CD4 count above 200 cells/µl. Of the 2,829 patients in the cohort, 502 chose to participate in a club. At the conclusion of the study, 12.8% of patients died or were lost to follow-up and 9.0% had virologic rebound. The median age was 33, 71% of participants were women, and 88% of patients were virologically suppressed at the initiation of the study. Adherence clubs consisted of groups of 15 to 30 patients who met for counseling and to collect their medication. Most patients who had the option to transition to the adherence club did so as it took less time to collect medications through the club than it did at the clinic. Medications were pre-packaged for each patient and brought to the meeting by the counselor. Patients in normal care who were less than 25 years old and who entered the study with a CD4 count of less than 50
cells/µl had the highest rate of death and loss to follow-up. Patients were more likely to be enrolled in a club if they had a higher CD4 count at study entry or during follow-up, were women, or had been on ART for longer than average. Adherence clubs improved adherence by decreasing loss to follow-up and virologic rebound (Luque-Fernandez et al., 2013). This model is currently being scaled up in Western Cape, South Africa (Wilkinson, 2013). (Gray IIIa) (treatment, adherence, support, South Africa)

- A study of 268 patients in South Africa found that support of a treatment buddy, community health workers or support group had better ART outcomes than those patients who did not. Treatment buddies reminded the patient to take ARV drugs and 75.9% of study participants reported that their treatment buddy helped their adherence. Community health workers provided emotional support and motivation for adherence. And 89.9% of support group members reported that the support group meetings helped them by sharing knowledge and experiences. Over 85% of patients rated treatment buddies, community health workers and HIV support groups as good or excellent. Of the 268 patients, 76.4% had CD4 counts over 200 after 24 months of ART (Wouters et al., 2009b). (Gray IIIa) (treatment, adherence, support groups, South Africa)

- In Vietnam, people living with HIV served as peer assistants to help other people navigate the steps from HIV diagnosis to enrollment in HIV outpatient care clinics. National guidelines in 2010 have resulted in community teams trained to support adherence, resulting in a rate of retention of 90% in some districts. In one district, antiretroviral therapy retention improved from 66% to 85% between 2009 and 2010 (WHO et al., 2011b). (Gray IIIb) (treatment, adherence, support groups, Vietnam)

- A study between 2008 and 2010 with 1,384 people living with HIV enrolled in 291 groups in Mozambique found that support groups led to increased adherence. ART distribution and monitored adherence was conducted by community groups in a model developed by Medecins sans Frontieres and provincial authorities. Patients who were stable on ART for six months were informed about the community ART group model and invited to form groups. Group members facilitated monthly ART distribution to other group members; provided adherence and social support; monitored outcomes and ensured that each group member had a clinical consultation once every six months. Group members visited the health center on a rotational basis, so that each group member had contact with health services at least once every six months. Group members were followed for 12.9 months. Of the 1,301 patients still in community groups after 83 transferred, 97.5% remained in care, 2% died, and 0.2% were lost to follow up. In other health settings in this area, up to one in five patients are lost to follow up. To join a community support group, patients had to be clinically stable on ART for at least six months and have CD4 counts over 200. Counselors trained the newly formed groups on their roles and responsibilities. Group members could still visit the health center for any reason at any time. At the facility, the group representative discussed each group member with a counselor or clinician, covering issues of adherence, clinical status, etc. The group monitoring form was reviewed. Upon return to the community, the group representative distributed medications and returned patient appointment cards and if needed, requested a group member to go to the health facility for follow up. All members for different community groups were invited every six months for a group session held either in the community or the health facility to discuss when to go to the clinic for unplanned consultations, patient education on TB, etc. CD4 counts are taken. The majority of community group members were female (70%). Median gain in CD4 cell count since initiation was 478.5. Of the patients, 3.5% decided to transfer back to conventional care (Decroo et al., 2011). (Gray IIIb) (treatment, adherence, support groups, Mozambique)

- A qualitative study of 18 women with four focus groups from 10 different support groups led by para-professionals in Rwanda found that the support group empowered them to become adherent: “I met with (support group) counselors and they told me how I will survive with HIV...I learned the importance of taking medicine on time...Before I attended, the doctors used to ask me if I was
taking the medicine at home and I used to say, “Yes, I take them” but I was lying to them.” (Walstrom et al., 2013: 98). (Gray V) (treatment, adherence, support groups, Rwanda)

- A qualitative study of 26 women in Thailand found that joining AIDS support groups provided emotional support. One woman stated: “Joining the group activity is good...(and) makes me have emotional strength that it is not only me who has got this disease in the world” (Liamputtong et al., 2012: 447). (Gray V) (treatment, adherence, support groups, Thailand)

- A qualitative study of 15 women living with HIV in Vietnam found that women in support groups expressed that they enjoyed a lot of benefits by participating in support groups, but also found that their additional knowledge made them fear treatment failure and whether ARVs would always be available to them (Nguyen et al., 2012). (Gray V) (treatment, adherence, support groups, Vietnam)

- A qualitative study of women living with HIV in Colombia with six in-depth interviews and five focus groups with 47 women found that participation in support groups was associated with higher adherence (Arrivillaga et al., 2011). (Gray V) (treatment, adherence, support groups, Colombia)

4. Counseling improves adherence.

- A meta-analysis of 19 randomized controlled trials including 1,839 patients found that one-on-one counseling given by health providers, with a median of two sessions, with each session lasting 60 minutes, with patients being more than one and a half times more likely to achieve 95% adherence, compared to controls. The effect was larger in studies where pills counts were used as compared to self-reporting (Simoni et al., 2006 cited in Vergidis et al., 2009). (Gray I) (counseling, health care providers, adherence)

- A review of 21 studies in Sub-Saharan Africa (including three randomized controlled trials; six mixed method studies; seven cohort studies; and five qualitative studies) on the roles and outcomes of community health workers found that community health workers effectively provided counseling and adherence support, as well as screening and referral for patients, enhancing uptake of HIV services and retention in care. Community health workers also reduced clinic wait times and reduced the workload of other health workers. Patients served by community health workers did not have increased mortality nor any differences in virological failure compared to patients served only in facilities. Studies found that community health workers in Uganda led to timely patient referrals, reducing delays in care (Alamo et al., 2012 cited in Mwai et al., 2013); improved patient flow at clinics in Lesotho (Joseph et al., 2012 cited in Mwai et al., 2013): and increased access and improved virological suppression in Uganda and Rwanda (Kipp et al., 2012; Rich et al., 2012 cited in Mwai et al., 2013). However, community health workers lacked adequate recognition, remuneration and involvement in decision-making leading to demotivation and attrition. Community health workers were defined as those having no formal professional or paraprofessional certificate or degree in tertiary education (Lewin et al., 2010 cited in Mwai et al., 2013). (Mwai et al., 2013). (Gray I) (treatment, adherence, community health workers, Sub-Saharan Africa)

- A randomized controlled trial with 297 patients living with HIV conducted from 2007 to 2009 who were ART-naïve in South Africa found that participants receiving intensive motivational counseling had similar rates of adherence to patients who received didactic adherence counseling. Participants were 43.1% male and virological suppression at nine months was achieved in 89.8% of those who received didactic counseling and 87.9% of those who received motivational counseling. Motivational counseling provided one-on-one interactive sessions and participant problem solving, including managed disclosure. Didactic counseling provided information and treatment literacy on stigma, nutrition, how ART is transmitted, the importance of adherence, side effects and resistance in three session but without engagement of individual issues faced by patients. Both groups received repeated adherence assessments, with tracking, tracing and pillboxes. Counseling was provided to any patient with problems or adherence concerns, with the additional counseling more
likely among those in the didactic arm (van Loggerenberg et al., 2014). (Gray II) (treatment, adherence, counseling, South Africa)

- A randomized trial with 301 patients in Kenya from 2006 to 2008 found that early adherence counseling during the first two months of ART initiation resulted in sustained, significant impact on adherence and virological treatment failure during 18-month follow-up. Patients were randomized to 15 minute counseling or three counseling sessions of up to 45 minutes each. Patients who received three counseling sessions were 29% less likely to have monthly adherence under 80% and 59% less likely to experience viral failure compared to those who received 15 minutes of counseling. Counseling was not associated with mortality, possibly due to short follow-up time. Counseling was based on a model of successful antiretroviral adherence developed by the University of Washington and adapted for Kenya with a written standardized protocol and lasted from 30 to 45 minutes per session. The first session addressed barrier and taught patients the risks of poor adherence; the second session on a separate day reviewed the patient’s understanding and a review of the patient’s readiness to initiate ART; and the third session addressed practical and personal issues that the patient experienced on ART. Three interactive sessions, two prior to ART initiation and one session following one-month ART initiation resulted in significant outcomes 18 months later. For those who did not receive counseling, the study pharmacist explained the side effects of medication and problems associated with poor adherence in a 15-minute session prior to dispensing ART. Compared to the costs of treatment failure, employing counselors can represent significant cost-saving (Chung et al., 2011). (Gray II) (treatment, adherence, counseling, health care providers, Kenya)

- A multicenter cohort study was conducted in South Africa from 2004 to 2011 to evaluate the effect of community-based adherence-support on adherence among ART patients. The patients who received community-based support had a 35% reduction in mortality and a 37% reduction in loss to follow-up as compared to patients that did not receive community-based support. From 57 care facilities, 66,953 patients were included; 29.4% of patients received community-based support while 70.6% did not. Patients were initially enrolled on ART when their CD4 count fell below 200 cells/µl. After April 2010, the criteria was expanded to include enrollment on ART when CD4 count fell below 350 cells/µl. All adults not previously enrolled on ART with documented demographics and at least one day of follow-up were included in the study. Community-based adherence-support included a paid patient advocate doing an initial home visit, weekly visits for the first month, and then visits at least every three months. If the patient did not attend clinic visits regularly, the frequency of home visits by the patient advocate was increased. Patients who were labeled “very important” included pregnant, ill, or TB co-infected patients, and were visited at least once a month. Patient advocates provided services including counseling, adherence checks, referrals, health promotion education, and screening for opportunistic infections. Patient advocates were trained in an initial 3-week course, subsequently participated in a 5-day refresher course every year, and were assigned 80-120 ART patients. Patients who received community-based support and patients who did not receive community-based support had access to site-based adherence counseling at some clinics. Patients who did not receive community-based support who missed appointments were tracked by phone or re visited at home by a district tracing team. Patients who received community-based support on average had more advanced HIV upon initiation of treatment, had a slightly higher baseline CD4 count, were more likely to have a TB co-infection, and were enrolled on ART during the more recent study period. After 5 years, 13.2% patients who received community-based support were lost to follow-up, as compared to 17.7% of patients who did not receive community-based support. The mortality rate was 9% in patients who received community-based support, while mortality was 10.6% in patients who did not. Low base-line CD4 count was strongly associated with mortality in both groups of patients. After 6 months of ART, viral suppression occurred in 76.6% of patients who received community-based support, while only 72% patients with no community-based support had viral suppression. The community-based adherence-support program improved adherence with demonstrative reductions in loss to follow-up
and mortality, and improved rates of viral suppression (Fatti et al., 2012). (Gray IIIa) (treatment, adherence, counseling, community, South Africa)

- An ecologic study was done on HIV clinics initiating HIV-positive individuals on ART from 2004 to 2008 in Côte d’Ivoire, Ethiopia, Kenya, Lesotho, Mozambique, Nigeria, Rwanda, South Africa, Tanzania, and Zambia to evaluate the effect of different adherence support services on attrition following ART initiation. The study found that clinics with counseling services, educational materials, reminder tools, and food rations had significantly lower attrition than clinics that did not have these services. The study used data from 349 clinics that provide free ART following the national HIV treatment guidelines in each specific country. This included data from 232,000 patients, 83,389 of which also had 6- and 12-month follow-up data that was used for cohort analysis. The attrition measure included death, loss to follow-up, and discontinuation of ART. A total of 300,700 person-years of data was collected. Fifty-nine percent of patients were women. On average, clinics reported four adherence support services (93% had at least one and 83% had more than two). The most common adherence support service, counseling, was reported in 88% of clinics. The least common adherence support service was food rations, 17% of clinics reported food ration services. Overall, 72% of the patients were in care at the same clinic at the end of the follow-up period. Nine percent transferred to another clinic, 6.3% had died, 0.9% discontinued ART, and 11.9% were lost to follow-up. The attrition rate was 14.2 per 100 person-years. Clinics that had less than 2 adherence support services had marginally lower attrition rates than those with 2 or more services. On-site support groups, peer educator programs, pharmacy support, and active patient outreach were not significantly associated with attrition. Clinics with less than 2 adherence support services had lower rates of loss to follow-up but not significantly lower rates of mortality as compared to their counterparts with 2 or more support services. In cohort analysis, pharmacy support services and active patient outreach were associated with lower patient attrition (Lamb et al., 2012). (Gray IIIa) (treatment, adherence, counseling, support, Côte d’Ivoire, Ethiopia, Kenya, Lesotho, Mozambique, Nigeria, Rwanda, South Africa, Tanzania, and Zambia)

5. Providing treatment support and literacy, including by HIV-positive peers and by providers, can increase adherence.

- A cross-sectional study was conducted at a hospital in Jakarta, Indonesia in 2012 to explore the factors associated with ART adherence. The study found that, “the level of social support experienced by ART-prescribed patients was positively associated with adherence,” (Weaver et al., 2014: 1). In total, 261 patients participated in the study; 74% were male, 54% were married, and 41% were unemployed. If the patient missed one or more doses of ART medication in the last four days or three or more doses of ART medication in the last three months, they were considered non-adherent. The difference in adherence between the male and female participants was minimal. The patients were also asked about their social support. A reported 52% of respondents had good social support, while 38% reported only some social support and 10% reported poor social support. Multivariate analysis demonstrated that the level of social support reported by respondents had an effect on adherence, where, “greater levels of social support significantly improve adherence,” (Weaver et al., 2014: 3). (Gray IIIb) (treatment, adherence, support, literacy, Indonesia)

- A qualitative study of 79 people (64.6% women) living with HIV in Swaziland out of 2,500 clients served by a faith-based organization that provided community home-based care found that 92% stated that with care supporters, their health had improved. From 2008 to 2011, 1,001 clients were on ART and the mortality rate of clients declined from 35.3% to 14.8% (Van Wyngaard, 2013 cited in Root and Whiteside, 2013). Caregivers’ multiplied the number of constructive and relevant conversations around HIV. Patients stated that they had commenced ART because of their caregivers’ encouragement. Caregivers encouraged clinic follow up when patients experienced medication side effects. One patient stated: “Now I’ve got the knowledge of (how to live) from the
Caregivers provided ongoing instruction regarding ART adherence. One patient noted that caregivers “helped me take the pills: eat first, wait, then take pills…I used to vomit” (patient cited in Root and Whiteside, 2013: 4). Care supporters enhanced treatment uptake and literacy, reduced stigma and assisted patients to challenge social pressures to stop ART. Caregivers, with the patients’ permission, helped patients disclose to family members. With caregiver encouragement, one woman stated to men in her community that she should stop taking ART: “No, I will continue taking my medications” (patient in Root and Whiteside, 2013: 5). Caregivers also encouraged breaking down denial of HIV; other patients who were disparaged by community members for taking ARVs stated: “I am very fortunate because I know my HIV status. What about you?” (Patient in Root and Whiteside, 2013: 6). Care supporters were nearer to us each and everyday...And we are open to speak to the care supporter about things that we are afraid to speak to the nurses about” (Patient in Root and Whiteside, 2013: 6). Only 11% of health facilities in the area had a health worker trained in HIV; no health facility had internet access. Care supporters were trained for one week on HIV with a religious component and received no remuneration. Care supporters traveled in pairs. Of patients, 15% did not identify as Christian but all participants wanted Christian care givers, as they perceived them to have larger “hearts,” to be trustworthy and maintain confidentiality (Root and Whiteside, 2013) (Gray V) (treatment, adherence, counseling, support, Swaziland)

- A model developed by the Thai Network of People with HIV/AIDS (TNP+) which involved activists living with HIV trained in treatment adherence achieved success through a comprehensive and continuous care program in Thailand. HIV-positive activists had established such centers at one-third of hospitals by 2008. The model requires that HIV-positive activists ask permission from the hospital director, be assigned a room in the hospital for their work and hospital staff agrees that the activists can join the hospital’s HIV care and treatment team. One activist manages a caseload of 15 to 20 clients, recognizing common side effects of antiretroviral drug regimens, evaluate treatment adherence, and answer questions on prevention. Activities are supported by NGOs and TNP+. Activists are now accepted as co-providers of health care rather than passive receivers (Ford et al., 2009a). (Gray V) (treatment, adherence, support groups, Thailand)

- A prospective single arm observation study of low-literacy and low-income patients over a 12 month period in 2005 in Mozambique who were provided care by a multi-disciplinary team which educates patients about HIV transmission and prevention resulted in a 95% adherence level to HAART by 69.5% of 531 patients. An additional 16.8% reported taking between 90 and 95% of the pills prescribed, for a total of 86.4% of patients with adherence levels above 90%. Only 3.2% abandoned antiretroviral therapy. Physician, pharmacist and center coordinator each conduct counseling sessions with each patient. Peer support groups are held. Additional elements of the intervention include: health information groups and provision of illustrations on how to take HAART; nutritional support for the patient and the family, along with nutritional counseling; staff training on adherence strategies; home care; coordinator responsibility for patients’ adherence; and employing trained HIV-positive community health workers. Viral loads and pill counts assessed adherence. Over 94% of the 531 patients knew that they needed to take HAART each day at precise times for the rest of their lives, despite low levels of formal education, with over 32% being illiterate and over 41% having less than five years of schooling. Over 90% of patients said they had a good relationship with their physician. More than 94% of patients knew they could transmit HIV through sexual relationships. More than 96% took all of their pills in the three days prior to the interview and 92% of patients kept more than 95% of their appointments to collect HAART (Magnano San Lio et al., 2009). (Gray IIIb) (counseling, treatment literacy, adherence, Mozambique)

6. Pill counts and pillbox organizers increase adherence and are a low-technology empowerment tool.
A prospective cohort study in Kenya was done from 2009 to 2011 to examine the relationship between pill counts and adherence. Physicians conducted 1,236 unannounced pill counts during 1,818 clinic visits among 291 patients. The number of clinician initiated pill counts was positively associated with better adherence and better treatment outcomes. Patients who were HIV-positive, treatment-naïve adults were followed for at least one year. The patients were categorized into three categories based on the number of pill counts they received in 6 months: no pill counts, 1 to 3 pill counts, and more than 3 pill counts. The patients with no pill counts had a 75.9% adherence rate, the patients with 1 to 3 pill counts had an 83.9% adherence rate, and the patients with more than 3 pill counts had a 92.4% adherence rate. Further, there was a longer time to treatment failure for those with more pill counts. The patients with no pill counts had an average 220 days to treatment failure, the patients with 1 to 3 pill counts had an average 438 days to treatment failure, and the patients with more than 3 pill counts had an average 497 days to treatment failure. Of the 29.2% of patients that were treatment failures, 56.5% were virologic failures, 17.6% were deaths, and 25.9% were lost to follow-up. The physicians conducted pill counts at 68% of clinical visits, which were scheduled monthly. The number of clinician initiated pill counts in this study was positively associated with better rates of adherence and a decreased risk of treatment failure (Achieng et al., 2013). (Gray IIIb) (treatment, pill counts, adherence, Kenya)

A survey of 299, patients in Nigeria, 72.7% female, found that use of a pillbox increased self-reported adherence (Ukwe et al., 2010). (Gray IIIb) (treatment, pillbox organizers, adherence, Nigeria)

Data obtained from an observational cohort of 245 people living with HIV from 1996 to 2000 in the United States showed that pillbox organizers were estimated to improve adherence by 4.1 to 4.5% and was associated with a decrease in viral load of .34-.37 \( \log_{10} \) copies/mL and a 14.2% to 15.7% higher probability of achieving a viral load of lower than 400 copies/mL, with statistically significant effects. “Pillbox organizers should be a standard intervention to improve adherence to antiretroviral therapy” (Peterson et al., 2007). (Gray IIIb) (treatment, adherence, pillbox organizers, United States)

Mobile phone text messages from health providers may improve adherence by providing patient support. Note: WHO notes the importance of national regulations to protect the privacy of those receiving text messages (WHO, 2013: 180).

A Cochrane review of Lester et al., 2010 and Pop-Eleches et al., 2011 (see studies below) found that there is high quality evidence from two randomized controlled trials that mobile phone text messaging enhances adherence to ART compared to standard care (Horvath et al., 2012). (Gray I) (treatment, adherence, mobile phones)

A randomized controlled trial was conducted on HIV-positive women in Brazil from 2009 to 2010 to assess adherence with a mobile SMS message program and their impressions and satisfaction with the program. The trial found that participants receiving the SMS messages consistently had better adherence rates by every measurement. Self-reported adherence resulted in an adherence rate of 84.62% for the control group and 100.00% for the intervention group. On the other hand, the counting pills method resulted in an adherence rate of 38.46% in the control group and 50.00% in the intervention group. Microelectronic monitoring indicated that 46.15% of the control group and 75.00% of the intervention group were adherent. In terms of acceptability, at the end of the study 81.81% of the intervention group believed that the SMS messages aided in treatment adherence, and 90.90% said that they would like to continue receiving the messages. The study group consisted of 21 HIV-positive women, and due to this small size, no statistical significance was able to be demonstrated. All study participants had to own a phone, have a viral load below 400 copies/ml for at least 3 months, and have a CD4 count above 200 cells/µL. Thirteen were allocated and completed the study in the control group, 8 were allocated and completed the study in the intervention group. There was no statistical difference in age or any baseline characteristic between
groups except that there were a higher proportion of married women in the control group. There were differences between groups in terms of drugs and alcohol; 53.84% of control participants reported drinking alcohol in the last 30 days while only 12.50% did in the intervention group. No participants in the control group reported using drugs while 50.00% in the intervention group reported drug use (including cigarettes, marijuana, cocaine, and ecstasy). All the women received routine care over a 4-month period, where they were required to attend monthly clinic visits to assess adherence as well as receive routine health checks. Three measures of adherence were collected to determine adherence at every monthly period: self-reported adherence, pill counting, and microelectronic monitors monitoring (which records when pill containers are opened and closed). The microelectronic monitors were only placed on one of the ARVs for each patient. The study authors note that measuring the adherence in the study as they did was very time consuming and doubled the time of the usual consultation. During the last visit (5th visit), after adherence checks, the women in the intervention group were interviewed about their impressions on receiving the text messages. SMS messages were sent to the intervention group 30 minutes prior to the time for the last required medication dose in a day. These messages were sent on alternative weekdays and on Saturdays and Sundays and included the message: ‘The UNIFESP informs: take good care of your health’. In terms of the impressions from the SMS messages, one participant in the intervention group thought the message should be changed daily and three participants thought the message should be sent closer to the medication time. Seven participants said it helped them remember to take their medication, three participants said that they felt that the medical center or someone else cared about them, and one participant said that the SMS messages allowed for family involvement in her treatment. Women noted that it was important to them that the text message just said to take care of their health so that their HIV serostatus was not revealed in case someone saw their phone (da Costa et al., 2012). (Gray II) (treatment, adherence, mobile phones, Brazil)

- A randomized controlled trial from 2007 to 2008 in Kenya with 438 patients who initiated ART found that 53% of participants receiving weekly text messaged reminders achieved adherence of at least 90% during the 48 weeks of the study, compared with 40% of participants in the control group who received standard care. Participants receiving weekly reminders were also significantly less likely to experience treatment interruptions exceeding 48 hours during the 48-week follow-up period than participants in the control group. Patients in the intervention group were provided a mobile phone and told that they could use it as they desired. All messages were less than 160 characters and did not specify HIV or ART in order to maintain confidentiality and were not timed to coincide with dosing schedules. A sample message was: “This is your reminder. Be strong and courageous, we care about you.” Every two months, patients in the intervention group received less than US$1 of phone credit and had to show their phone to clinic staff at every visit (Pop-Eleches et al., 2011). (Gray II) (treatment, adherence, mobile phones, Kenya)

- A randomized clinical trial with 538 patients in Kenya found that patients who received support via text messages from mobile phones significantly improved ART adherence and rates of viral suppression. Patients in the intervention group received weekly text (SMS) messages from a clinic nurse and were required to respond within 48 hours. Suppressed viral load was reported in 156 of 273 in the SMS group and 128 of 265 in the control group. Patients had to be able to access a mobile phone on a daily basis. Patients received the message “How are you?” (Mambo) and were instructed to answer that they were doing well (Sawa) or they had a problem (Shida). The clinical then phoned the patients who said they had a problem or who failed to respond to the text within 48 hours. Only 3.8% of weekly text messages identified a requirement for follow up by responding “Shida”. Participants were classified as virologically suppressed if their HIV RNA load at their 12-month visit was 400 copies per mL or less. No adverse event directly attributable to the mobile phone communication, such as breaches of confidentiality was reported. At the end of the study, 191 of 194 patients in the intervention group reported they would like the SMS program to continue. In addition, during the political turmoil and violence in Kenya after the 2007 presidential elections, mobile phones were used to request clinic staff assistance to new safe locales where drug refills could be obtained. The intervention was inexpensive, with each SMS costing about US$.05,
or $20 per 100 patients per month, and follow-up voice calls which averaged $3.75 per month (Lester et al., 2010). (Gray II) (treatment, adherence, mobile phones, Kenya)

- A cohort in India who had mobile phone adherence support was followed for a month in 2010. The support utilized both pictorial text messages and phone calls and the study assessed the perceived usefulness and acceptability of the program among HIV-positive individuals. The study found that 73% of the calls were received, 90% of the participants reported that the mobile reminders were helpful as adherence support, and despite 18% of participants reporting that someone else had inadvertently received their call (and 13% of participants reporting that someone had received their message) no participants reported discomfort or stigma. Eighty-seven percent of the participants reported that they preferred the calls as reminders over the text messages. A total of 744 calls were made to 150 people over the course of a month (139 people completed the follow-up visit). Participants received both an interactive voice response call and a pictorial image through SMS messaging. The call was weekly and the participants were asked to report ‘1’ if they had adhered to their medication the previous day and ‘2’ if they had not. If the call was not received up to three calls were made in the next 24 hours in an attempt to reach the patient. The pictorial text message was delivered once a week and three days after the call. After a month the participants were administered a questionnaire about their experience with the intervention. Seventy-three percent of the participants were men, 85% were educated beyond primary school, and 83% were employed. The median CD4 count was 435 cells/µl and women and the unemployed were more likely to report sharing a cell phone with another individual (86% of participants owned their mobile phone). Of the completed calls, 77% of the responses were ‘1’ (that participant adhered to their regimen the previous day), 2% were ‘2’ (the participant had not adhered to their regimen the previous day), and 21% pressed an incorrect number or did not press a number. For the SMS messages, 59% reported viewing all of the messages and 15% of participants reported never viewing the pictorial message. The participants were more likely to receive the call than the text message, and 87% of participants preferred the call over the text message. The study authors note that there are benefits to both options, writing that, “SMS has the capability of deliver a message regardless of the surrounding circumstances, i.e., SMSs are silent and can be received in situations where it is not appropriate to have a conversation. On the other hand, SMSs leave a distinct trail where [interactive voice response] may be more discreet,” (Sidney et al., 2012: 616). While 99% of participants reported knowing how to make or receive a call, only 86% knew how to receive an SMS message and only 47% knew how to send one (Sidney et al., 2012). (Gray IIIb) (treatment, adherence, mobile phones, India)

- A cross-sectional study in rural Uganda assessed the impact of using mobile phones to increase clinic attendance to collect refills of ARVs. Of 276 patients surveyed, 177 (64%) had access to mobile phones and all but one were willing to be contacted for missed visit reminders. Of 560 total scheduled clinic appointments for the 176 patients followed for 28 weeks, 11% of visits were missed. In 79% of episodes in which visits were missed, patients presented for treatment within a mean duration of 2.2 days after mobile phone contact. Privacy and confidentiality were not considered a problem. Total cost for using mobile phones during the 28 weeks was US$14. Adherence was also assessed every four weeks using clinic based pill counts. “Women constituted the majority of clients surveyed, while men had more access to mobile phones” (Kunutsor et al., 2010: 1349). (Gray IIIb) (treatment, adherence, mobile phones, pill counts, Uganda)

8. Community-based antiretroviral therapy programs may be as effective for adherence as facility-based programs, with lower costs for both patients and services.

- A global review of studies, including one in Uganda, found an association between decreased viral load and community-based ART programs. The review found 21 studies (not listed); 15 of which were high quality, randomized controlled trials or quasi-experimental programs. The remaining studies were high quality program evaluations (Amanyeiwe et al., 2014). (Gray I) (treatment, community-based care, Uganda)
A systematic review found that community-based antiretroviral programs may be as effective as facility-based programs, with lower costs for both patients and services. Six different programs, summarized in 18 different articles, took place in Uganda, Kenya and Mozambique between 2006 and 2013. In one study in Uganda, community health workers delivered ART at home, provided adherence support, detected side effects and referred sick patients to clinics. Each community health worker was responsible for 40 patients and had six weeks training, along with a basic salary, motorbike and cell phone. The cluster randomized controlled trial found that at 36 months on treatment, the viral load was below 500 for 84% of patients in community based ART and 83% for facility based patients. After 36 months, loss to follow up was 1% for community based patients and 2% for facility based patients; mortality was 14% for community based patients and 13% for facility based patients, with costs lower for community based patients (Jaffar et al., 2009 cited in Decroo et al., 2013). A study in Kenya found that at 12 months, of the 96 patients randomly assigned to the community based arm, 5% were lost to follow up, 1% had died and 89% had an undetectable viral load. Among the 112 patients receiving care in the health facility, 5% were lost to follow up, none died and 86% has an undetectable viral load. Those in the community based arm had 50% fewer health facility visits. Community health workers, including people living with HIV, had a seven-day training followed by a two month practicum and was responsible for 20 clinically stable patients each (Selke et al., 2010 cited in Decroo et al., 2013). Community-based antiretroviral therapy reduced costs for patients but also was more cost-effective for health services. “…Community participation requires an approach which is contradictory to the dominant provider-driven development of health services” (Decroo et al., 2013: 176). (Gray I) (treatment, adherence, community-based care, Uganda, Kenya, Mozambique)

A review of the published literature on the impact of community support services was done to evaluate the power of a diverse array of community support providers on ART program delivery and outcomes. Data was used from studies published from 2004 to 2012 and located in Uganda, Ethiopia, South Africa, Brazil, Malawi, Namibia, Lesotho, Kenya, Rwanda, Tanzania, Zambia, Nigeria, Haiti, Guyana, Botswana, Peru, and Mozambique. The review found that community support initiatives can broaden the access of programs, as well as have a positive impact on adherence, health outcomes, patient retention, and mortality. Challenges that the study authors note regarding success of scale-up of ART programs in many areas include, “(1) lack of integration of ART services into the general health system; (2) the growing need for comprehensive care to address the psychosocial and economic dynamics of HIV/AIDS; (3) the need to empower patients on ART towards self-management; (4) the importance of defaulter tracing to improve retention in care; and (5) the crippling shortage in human resources for health,” (Wouters et al., 2012: 2). The study authors argued that community support could help alleviate some of these challenges. Thirty publications were analyzed, including nine descriptive studies, five randomized controlled trials, four quasi-experimental studies, five cohort studies, and two qualitative studies. Community support ranged from community health workers who underwent short training courses and provided support to other health workers, to peer health workers who are HIV-positive and who counseled patients on adherence and health education, to field officers who supported drug delivery and monitored patients. Almost all studies reported positive impacts of community support through a diverse set of programs. Community support programs were shown to increase access to and coverage of ART programs at a facility level. Some studies also noted that community support providers could link HIV-positive patients to other parts of the health care system, thereby further integrating HIV services with other primary care services. Adherence levels were also demonstratively improved in many studies with the implementation of a community support program. Many studies demonstrated that with community support, a higher proportion of patients lowered their viral load and increased their CD4 counts. Some studies also demonstrated that loss to follow-up and mortality was decreased with community support services. The articles reviewed concerning directly-observed therapy for ART did not find any association between that form of community support and improved outcomes. Community services may also serve to empower patients and to take on the issues associated with having HIV that go beyond treatment (Wouters et
al., 2012). (Gray I) (treatment, community-based programs, Uganda, Ethiopia, South Africa, Brazil, Malawi, Namibia, Lesotho, Kenya, Rwanda, Tanzania, Zambia, Nigeria, Haiti, Guyana, Botswana, Peru, Mozambique)

- A global review of studies, including studies in Uganda and South Africa, found that providing ART through community volunteers, trained and supervised by a clinical officer, resulted in adherence equal to ART provided in clinic setting (Thompson et al., 2012) (Gray II) (treatment, community-based care, Uganda, South Africa)

- A retrospective cohort study was done on a group of individuals living with HIV starting a community-based HIV treatment program in Rwanda from 2005 to 2006. The community-based program included free ART with directly observed therapy at home, tuberculosis screening and treatment, nutritional support, a transportation allowance, other assistance for those in extreme socioeconomic conditions, electronic medical records, and patient support groups. The study found that 92.3% of people were retained in care at 2 years (5% were dead and 2.7% were lost to follow-up). The median CD4 count was to 336 cells/µl after 2 years, from 190 cells/µl at initiation. There were originally 1,041 people enrolled in the community-based ART program. People were initiated on ART according to national guidelines which stated that any WHO stage IV, stage III with CD4 count of less than 350 cells/µl, stage I or II with a CD4 count of less than 200 cells/µl would be started on ART. Co-trimoxazole was prescribed to all patients with a CD4 count of less than 350 cells/µl. Patients who had documentation of a transfer were considered retained in care (3.4% of the initial cohort). The cohort was 66.3% women and the mean age was 38 years old. Age of more than 50 years and enrollment in 2006 (the second year) were associated with attrition. Among women, initial clinical stage was not associated with retention in care (attrition was much more likely among men with HIV stage III or IV). The majority of the deaths occurred in the first year of treatment. Tuberculosis was diagnosed in 17.8% of patients, of whom 89.4% completed treatment, 7.6% died, 2.4% transferred to another clinic, and 0.6% defaulted. There was no association found between attrition and tuberculosis diagnosis. Only about one-fourth of participants had a viral load measurement taken, but 97.5% of those with the measurement had viral suppression at 2 years. The study authors estimate that the extra programs would cost an additional $630 per year per person for the first year and $340 per year per person for every following year (Rich et al., 2012). (Gray IIIb) (treatment, adherence, community-based care, Rwanda)

- A retrospective cohort study was done on patients starting first-line ART between 2003 and 2008 in South Africa to develop a cohort of patients switching to second-line treatment with a viral load less than 400 copies/ml. The cohort in a workplace-based program and a community-based program were evaluated to describe outcomes and predictors of viral suppression on second-line ART. This study found that high levels of viral suppression can be achieved in treatment programs, with much better adherence rates in the community-based program as compared to the work-based program. After the switch to second-line ART, 48.3% of the workplace patients and 72.0% of the community patients achieved viral suppression. Non-adherence was reported in 17.9% of workplace patients, compared to 1.4% of community patients. In the workplace program, having a lower viral load at switch to second-line treatment and younger age were associated with viral suppression at 15 months. In the community-based program, patients with a shorter duration of viral load above 400 copies/ml (viremia), patients with a higher CD4 count, and patients who transferred into the program on first-line ART were more likely to achieve viral suppression. Of the 14,779 patients who initiated ART in the given period, 205 in the workplace program and 212 in the community program were switched to second-line treatment. Patients in the workplace had a median age of 43 years, 91.7% were male, and initiated ART at higher CD4 counts than the patients in the community-based program. Patients in the community-based program were 38.7% male and the median age was 36 years. Patients in the workplace program also had, on average, a longer duration of viremia. The workplace program operated in 56 clinics serving mostly mining companies. In the workplace program, employees were eligible for ART if they had WHO stage IV, a CD4 count of less than 250 cells/µl, or WHO stage III and a CD4 count of less than 350 cells/µl. The
9. Decentralization and integration of HIV services may increase adherence and early access to ART. [See also Structuring Services to Meet Women’s Needs]

- A Cochrane review of 16 studies published from 1996 to 2013 in Malawi, Ethiopia, Uganda, Kenya, Swaziland, South Africa, Lesotho, Mozambique, Rwanda, Tanzania, Thailand, and Nigeria was undertaken to assess the effects of various models of decentralized HIV treatment on initiation and maintenance of ART. The type of care was categorized as partial decentralization (where ART is initiated at a hospital and maintained at a health center), full decentralization (where ART is initiated and maintained at a health center), and community ART provision (where ART is initiated at a health center or hospital and maintained in the community). The outcome measured was ‘attrition’, which included loss to care and mortality. The review of four studies with 39,090 patients in total found that in a partially decentralized system, there was less attrition and fewer patients were lost to care after one year. The review of four studies with 56,360 patients in a fully decentralized system found that there was no difference in attrition from other models. ARVs started at a hospital and maintained at a health center had the least loss to follow-up. Finally, a review of two studies with 1,453 patients in a community ART provision system found that there was no difference in death or loss to care as compared to patients who received care at a health center. None of the decentralized systems were found to lead to worse health outcomes. Two of the studies used were cluster-randomized trails and the remaining 14 were cohort studies. This review demonstrated that different models of decentralization can lower attrition and loss to follow up and none led to worse health outcomes for the patients (Kredo et al., 2013). (Gray I) (treatment, health facilities, Malawi, Ethiopia, Uganda, Kenya, Swaziland, South Africa, Lesotho, Mozambique, Rwanda, Tanzania, Thailand, Nigeria)

- A systematic review to evaluate programs to improve linkage to care or retention in pre-ART care until initiation of ART was conducted based on studies from Cambodia, India, Kenya, Malawi, Mozambique, Rwanda, South Africa, Swaziland, Uganda, and Zambia. The study found several interventions that improved retention in care including integration of care and peer supporters to improve linkage to care, medical incentives to improve retention, and point-of-care CD4 testing and food incentives to improve rates of completion of ART eligibility assessment and initiation. Twenty-four studies conducted from 2004-2012 were used in the analysis. The studies all included data on interventions provided before initiation of treatment with the goals of improving linkage or retention in pre-ART care or initiation of ART. The systematic review...
included seven randomized controlled trials, seven observational studies with control groups, and ten pre/post studies. Interventions tested included: point-of-care CD4 testing, service integration (mostly HIV services with antenatal care), health systems interventions including improved communication, referral, and treating, and incentives (food and monetary). Most studies included data on completion of ART eligibility screening or ART initiation; fewer reported on linkage to care. Packages of health system interventions that improved referrals, communication, and teaching improved ART initiation by 15-27% in three studies. Point-of-care CD4 testing improved rates of patients completing ART eligibility assessment and ART initiation in multiple studies. Point-of-care CD4 testing had a less meaningful impact on retention in pre-ART care and on linkage to care. Peer support and counseling following HIV testing was found to increase linkage to care in three studies. Food incentives in India were found to lessen time to ART initiation and increase the proportion of people retained in pre-ART care. Medical incentives in the form of co-trimoxazole was found to increase pre-ART retention in Kenya. Overall, this systematic review demonstrated that minimizing patient facility visits, providing counseling and peer support, and providing incentives may improve rates of retention in pre-ART care and rates of ART initiation (Govindasamy et al., 2014a). (Gray I) (treatment, health services, Cambodia, India, Kenya, Malawi, Mozambique, Rwanda, South Africa, Swaziland, Uganda, Zambia)

- A retrospective cohort study of those over age 18 of 17 facilities with 4,147 patients from Tanzania, Uganda and Zambia found that community ART dispensing had significantly less attrition than other types of facilities. Patients started ART between 2003 and 2010 and 64.4% were female. Government, NGO and faith based facilities were included in the analysis. Four programs used community-based distribution of ARV drugs for stable patients. In sites with community ARV drug distribution, attrition proportions among both men and women were about 50% smaller compared with women in sites without community distribution (Koole et al., 2014). (Gray IIIa) (treatment, adherence, Tanzania, Uganda, Zambia)

- Four approaches developed by Médecins Sans Frontières to simplify ART delivery for stable patients on ART through community-supported models of care were assessed: 1) appointment spacing for clinical and drug refills in Malawi; 2) peer educator-led ART refill groups in South Africa (Luque-Fernandez et al., 2013); 3) a community ART distribution point in the Democratic Republic of Congo; and 4) patient-led community ART groups in Mozambique. All programs reduced the burden for patients via reduced travel time and reduced lost income and the burden on the health system via reduced patient volume. The retention in care was high for all four programs: 1) 94% of patients retained at 36 months in appointment spacing system in Malawi; 2) 97% at 40 months in a peer education program in South Africa; 3) 89% at 12 months in a community ART distribution point programs in the Democratic Republic of the Congo; and 4) 92% at 48 months in community ART groups in Mozambique. Separating ART delivery from clinical assessment was found to benefit both patients and programs in these diverse settings. In Malawi, 8,528 patients between 2008 and 2013 were enrolled in an appointment system where stable patients received ART in the community and only attended clinical visits once every 6 months. In South Africa from 2007 to 2011, 502 patients in adherence clubs where groups of around 30 patients met every 2 months for general health assessment and to pick up medication were evaluated against 2,327 patients in standard care. In the Democratic Republic of the Congo from 2010 to 2013, 2,162 patients were followed who had access to community ART distribution points where ART was distributed to stable patients at locations managed by people living with HIV. These distribution points were closer to the patient’s homes (saving the patient’s time and money) and also provided adherence support and basic health checks. In Mozambique, 5,729 community ART group members were followed from 2008 to 2012, where members were organized into groups of 6 and alternated which of the six patients went to the clinic to pick up medication for all six patients while having their own clinical check-up. These diverse programs and settings all separated ART delivery from the clinical assessment of the patient, in order to make the ART more accessible. In every case, the rates of retention were higher in the community-supported models than the control group (when available) or other published local data (Bemelmans et al., 2014). (Gray IIIa)
A study was done on two rural hospitals with twelve nurse-led health centers in Lesotho to compare outcomes of patients starting ART between facilities. The study found that the health centers had fewer early losses and similar long-term retention to care as the hospitals. When stratified by sex, the rates for women were similar between the hospitals and health centers; however, men had a higher retention to care at health centers as compared to hospitals. There were 3,747 patients above 16 years old that initiated ART at the hospitals or health centers from 2003 to 2011. Of these patients, 54.5% started ART at one of the health centers and the remaining patients started treatment at the hospitals. The hospitals were staffed with physicians and provided basic lab services. The health centers were staffed with nurse-clinicians, nurse-assistants, and lay or community counselors. The counselors provided HIV counseling and monitoring and traced patients that were lost to follow-up. The nurses initiated ART and managed the clinical monitoring of the patient. Retention in care, no follow-up (not returning after initiation of ART), and lost to follow-up (not returning to facility for 6 months after at least one follow-up visit) were all measured as part of the analysis. All patients initiating care in Lesotho are given a unique national identifier number, which is used in the instance of transfer from one center to another. At health centers retention to care was 68.8% at three years and at hospitals retention to care was 64.1% at three years. Three-year retention for women was 69.4% in hospitals and 68.7% in health centers - a difference that is not statistically significant. For men, three-year retention was 54.7% at hospitals and 68.8% at health centers. Men who were treated at health centers were significantly more likely to be retained in care at three years. Among women, 2.9% of hospital patients and 1.8% of health center patients had no follow-up visit. Among men, 2.9% of hospital patients and 1.7% of health center patients had no follow-up visit. The proportion of patients who died or were lost to follow-up were slightly lower in health centers as well. The proportion of patients who died was 10.1% at health centers and 13.5% at hospitals. The proportion of patients who were lost to follow-up were 12.7% at health centers and 13.9% at hospitals. The health center enrollee population did have less advanced disease and better immunological status. The only statistically significant difference was the rates of loss to follow-up for men between the health centers and hospitals. The study authors hypothesize that this difference, “may be employment related,” as many men, “work as subsistence farmers or as labourers…the easier accessibility of [health centers] may be of particular benefit to men,” (Labhardt et al., 2013: 7). (Gray IIIa) (treatment, adherence, health facilities, Lesotho)

Longitudinal analysis of HIV patients from 2001 and 2008 was conducted on 4,322 patients who received centralized and 11,090 patients who received decentralized care in rural Malawi and found that program attrition over two years was lower among patients receiving decentralized care (9.9 per 100 person years, compared to 20.8 per 100 person years), with no statistically significant differences in one-year levels of viral suppression observed between the two health care levels. Routine CD4 counts were conducted annually, with viral load testing only if a provider suspected treatment failure. Median CD4 cell counts were higher in decentralized facilities, meaning that patients were accessing care earlier in decentralized facilities, possibly due to reduction of patient travel time and costs. A cross-sectional survey of 312 patients in centralized and 390 patients in decentralized care was also conducted in 2009. Between 2001 and 20002, 78.5% of ART initiation took place at the centralized level; by 2008, 86.5% occurred in health centers. In each time period, higher proportions of men were initiated on ART in centralized rather than in decentralized facilities (McGuire et al., 2012). (Gray IIIa) (treatment, adherence, Malawi)

Retrospective cohort data from vertical and integrated Médecins sans Frontières programs in the Central African Republic, Côte d’Ivoire, the Democratic Republic of the Congo, Ethiopia, Nigeria, the Republic of the Congo, Uganda, Zambia, and Zimbabwe was used to compare the survival probabilities between programs from 2003 to 2010. The review showed that after adjusting for baseline population characteristics, there were similar outcomes for mortality and lower risk of loss to follow-up in the integrated programs compared to the vertical programs.
Vertical programs were programs that specifically treated HIV and integrated programs provided comprehensive health care including HIV services. Greater program experience was shown to be protective against death, although risk of loss to follow-up increased in programs with greater experience. Initiating ART at WHO stage IV disease was the characteristic most associated with death. A total of 15,403 HIV-positive people were followed in this analysis; with 14,124 patients in 7 vertical programs and 1,279 in 10 integrated programs. The process for HIV testing and treatment was uniform across the different programs. The study authors noted many reasons that integrated HIV programs may have potential advantages over vertical programs, including, “increasing the access of patients to HIV care in areas where vertical HIV programs may not be feasible; supporting retention in care by bringing services closer to patients… normalizing HIV as one illness among many, with potential stigma reduction; [and] allowing the treatment of patients for multiple conditions in the same facility by the same staff,” (Greig et al., 2012a: e92). Patients older than age 15 years and who had more than 6 months of follow-up time were included in the analysis. Vertical programs had 64% female patients compared to 71% in integrated programs. Vertical programs also had a lower proportion of patients classified as WHO clinical stage IV at ART initiation, 18% compared to 36% in integrated programs. Average CD4 count at ART initiation was higher at the integrated program, but CD4 measurement was not uniformly measured in the integrated programs. Without adjusting for these variables, the proportion of patients who died was lower in vertical programs. After multivariate analysis, the adjusted hazard of death was similar in both programs. The integrated programs also had a 29% lower risk of loss to follow-up when compared to the vertical programs. The study authors noted also that, “a standard package of protocols and training materials helped staff, as did the engagement of an experienced HIV clinician to help start the program and train staff,” (Greig et al., 2012a: e96). (Gray IIIa) (treatment, adherence, health facilities, Central African Republic, Côte d’Ivoire, the Democratic Republic of the Congo, Ethiopia, Nigeria, the Republic of the Congo, Uganda, Zambia, and Zimbabwe)

**Promising**

10. Frequent viral load monitoring can result in better health outcomes, including improved adherence and early identification of drug resistance.

- A meta-analysis was done to examine the efficacy of viral load monitoring as a tool to identity patients who need adherence interventions, and their subsequent outcomes with implementation of these interventions. Eight studies published from 2004 to 2013 in South Africa, the United States, Thailand, Mali, Burkina Faso, Swaziland, India, and France were included in analysis. Five of the studies, which reported percentages of patients with viremic resuppression, had a combined resuppression rate of 70.5% after the implementation of an adherence intervention following viral load testing. The remaining 3 studies all reported declines in mean viral load. Viral load monitoring identified patients who experienced an increase in viral load after previous suppression and who benefited from an adherence intervention. Patients in need of adherence interventions and those in need of second-line therapy could be identified through virological monitoring. Six of these studies were retrospective cohort studies and 2 were prospective cohort studies. Follow-up periods ranged from 3 months to 4 years. The threshold of viral suppression ranged from less than 50 copies per milliliter to less than 1,000 copies per milliliter. There was also variability in the adherence interventions, which included peer support, adherence counselors, peer counselors, educational sessions, home visits, adherence support tools, and short-term directly observed therapy. Although there was a good amount of variability between each cohort, the rates in the five studies reporting on proportion of patients resuppressing after an adherence intervention ranged from 54.2% to 89.1%. The remaining 3 studies reported significant declines in mean viral load. All studies showed that a majority of patients experienced resuppression with adherence interventions. When viral load testing began later, more than 60% of patients had already developed resistance mutations, suggesting that early viral load monitoring is vital to identify patients in need of additional adherence interventions. Studies showed that 78% of patients suspected of failing
second-line treatment experienced viral resuppression with adherence interventions, which was particularly important where third-line treatment options continue to be expensive and not widely available (Bonner et al., 2013). (Gray IIIb) (treatment, adherence, viral load monitoring, South Africa, the United States, Thailand, Mali, Burkina Faso, Swaziland, India, and France)

- A meta-analysis and systematic review of studies published between 2001 and 2009 on resistance patterns of the most commonly used ART regimens showed a higher resistance at 2 years in patients whose viral loads were less frequently monitored. A total of 8,376 patients Cameroon, Haiti, Malawi, South-Africa, Uganda, Zimbabwe, Europe and Canada were included in the studies. Group comparisons were made based on viral-load monitoring frequency: infrequent or none versus frequent. Resistance at virological failure to NNRTI in patients monitored at intervals of more than 3 months or none was 88.3% compared with 61% in patients monitored more frequently. Other mutations (thymidine analogue and lamivudine) were also higher in those who received no monitoring or the less frequently monitored group of patients. Mutations in all of the three classes of commonly used drugs in resource limited countries were substantially higher in those with virological failure in patients on NNRTI-based first-line ART for which viral load monitoring was absent or infrequent compared to patients who were monitored intensively (Gupta et al., 2009). (Gray IIIb) (treatment, adherence, viral load monitoring, Cameroon, Haiti, Malawi, South Africa, Uganda, Zimbabwe, Europe and Canada)

- A study conducted in Asia (the TREAT Asia Observational Database) found that viral load testing at intervals of less than annual frequency increased disease progression with poorer prognosis at low-income sites. Data of 2,333 patients from more than 11 Asian countries initiating on HAART since 2000 was analyzed. Sites were categorized according to the World Bank country income criteria as high-income or low-income and a yearly frequency of VL testing (3 or more, 1 to 2 or less than 1) or CD4 measurements (3 or more and less than 3). Low-income sites contributed to 61% of the eligible patients. Women constitute 35% of the low-income and 20.1% of high-income site patients. Patients at low-income sites and with sites reporting less frequent viral load testing had a poorer prognosis. Less than 1 viral load testing per year was significantly associated with higher rates of progression to CDC class C event or death. Patients at sites with less than annual reported viral load testing had lower odds of achieving virological suppression at 12 months than high-income sites which reported viral load testing frequency of 3 or more per year. In conclusion, low measures of site resourcing were associated with 35% increase in progression to AIDS and hence poor outcomes in patients from sites with viral load testing with intervals of less than once per year (Oyomopito et al., 2010). (Gray IIIb) (treatment, adherence, viral load monitoring)

11. Early active follow up when patients miss appointments may increase adherence.

- A study of a high risk express care program for 635 patients who were just initiating ART or who had a CD4 count of less than 100 in Kenya between 2007 and 2009 found that those enrolled in the high risk express care program were much more likely to be alive and in care following ART initiation for up to two years later. Following ART initiation by a clinical officer or physician, a nurse was responsible for interim weekly visits either physically or by phone for a period of three months, with a monthly visit by the patient to a clinical officer or physician. Patients in the high-risk express care program did not need to wait in any lines but could go directly to one-stop care. Nurses followed up any patient who missed an appointment (Braitstein et al., 2012). (Gray IIIa) (treatment, adherence, Kenya)

- A treatment program in Malawi that initiated active follow up when ARV patients were three weeks overdue for their appointments reduced the loss to follow up by 59% among 1,158 loss to follow up patients who had not died, transferred out or declined an interview (Tweya et al., 2010). (Gray IIIb) (treatment, adherence, Malawi)
7B. Gaps in Programming—Treatment: Adherence and Support

1. Interventions are needed to reduce barriers to treatment adherence and to understand how these differ by sex.

2. Interventions are needed to increase adherence for adolescents.

3. Major evidence gaps exist on adherence-enhancing interventions for long-term effectiveness and at higher CD4 counts.

4. Further operations research is needed on the optimal collaboration between HIV treatment facilities and community-based organizations, including cost-effectiveness data.

5. Legislation and enforcement of legislation that prohibits employment discrimination against people living with HIV is needed so that accessing HIV care is not seen as jeopardizing one’s livelihood.

6. Additional efforts are needed in implementing viral load monitoring to increase adherence.

7. Research is needed on what different factors affect adherence among men and women.

8. Specific additional adherence support is needed for those who initiate ARVs at CD4 counts above 250.

9. Increased information on an ongoing basis is needed concerning availability of support groups for people living with HIV.

10. Strategies are needed to address sub-optimal adherence during switch between first- and second-line ART.

11. Interventions are needed to reduce drug resistance, particularly among those who are treatment naïve. Third line regimens may be needed in some resource limited settings.

12. Interventions are needed to enhance counseling to successfully prepare patients for lifelong therapy.

13. Interventions are needed to address the adherence of patients who fast as part of religious practice.

1. **Interventions are needed to reduce barriers to treatment adherence and to understand how these differ by sex.** Increased research is needed to understand the most effective strategies to increase adherence. Studies found that a number of barriers that impact treatment adherence, such as violence, stigma, transport costs, childcare, forced migration, the need for food, the need to hide their medication from their male partners and changes in body image. Screening and treatment for depression may improve adherence, although some studies have shown mixed results. A review found that adherence differs by sex, but with little disaggregation for which factors affect women. Data collection should be more nuanced and not assume that women fall into static groups. A study of people living with HIV who disengaged from ART found that harsh and disrespectful treatment by providers, as well as competing work and livelihood demands, lack of funds for transport, etc. made attendance at ART clinics challenging.
• Gap noted, for example, in a review of evidence globally (Katz et al., 2013; Govindasamy et al., 2012; Mills et al., 2012b; Mills et al., 2012d; Mills et al., 2006; Dilmitis, 2014) and for high-income countries, including Hong Kong, Peru and Brazil (Puskas et al., 2011); a review of evidence for middle- and low-income countries (Nachega et al., 2010c; India (Joshi et al., 2014; Nyamathi et al., 2011; Bachani et al., 2010); Southern Africa (Kagee et al., 2011); Nigeria (Smith and Mbakwem, 2010); Guatemala (Campbell et al., 2010b); South Africa (Fisher et al., 2014; El-Khatib et al., 2010); Brazil (Campos et al., 2010); Uganda (Weiser et al., 2010; Siu et al., 2012); Burundi (Renaud et al., 2011); Tanzania (Layer et al., 2014; Roura et al., 2009); Zambia (Murray et al., 2009; Sasaki et al., 2012); China (Li et al., 2009; Sabin et al., 2008; Williams et al., 2014); Uganda, Tanzania and Botswana (Hardon et al., 2007); globally for PEPFAR-supported countries (IOM, 2013); Malawi (Pinto et al., 2013); Pakistan (Tahir and Uddin, 2014).

2. Interventions are needed to increase adherence for adolescents. Multiple studies from developed and developing countries reported young age as a risk factor for treatment interruption and that adolescents were less adherent to antiretroviral therapy than adults.

• Gap noted, for example, in South Africa (Nachega et al., 2009; Kranzer et al., 2010 cited in Kranzer and Ford, 2011); in the United Kingdom (Mocroft et al., 2001 cited in Kranzer and Ford, 2011); French Guiana (Nacher et al., 2006 cited in Kranzer and Ford, 2011); Europe, Argentina, and Israel (Holkmann Olsen et al., 2007 cited in Kranzer and Ford, 2011); Canada (Moore et al., 2009 cited in Kranzer and Ford, 2011).

3. Major evidence gaps exist on adherence-enhancing interventions for long-term effectiveness and at higher CD4 counts. A rapid systematic review by WHO found that while ART requires life-long therapy, the majority of studies have lasted two years or less.

• Gap noted globally (Chaiyachati et al., 2014; Thompson et al., 2012); in Asia and Africa (Gabillard et al., 2013).

4. Further operations research is needed on the optimal collaboration between HIV treatment facilities and community-based organizations, including cost-effectiveness data. A review of the global evidence found that more information is needed on which interventions are most effectively provided in communities as compared to HIV treatment facilities, and how a patient’s integrated needs can be best met as a continuum of care.

• Gap noted globally (Amanyeiwe et al., 2014).

5. Legislation and enforcement of legislation that prohibits employment discrimination against people living with HIV is needed so that accessing HIV care is not seen as jeopardizing one’s livelihood. Studies found that those who feared that they would lose their employment if found to be taking ARVs discontinued treatment.

• Gap noted, for example, in South Africa (Longinetti et al., 2014); Zambia (Musheke et al., 2012; Sasaki et al., 2012); Uganda (Siu et al., 2012).

6. Additional efforts are needed in implementing viral load monitoring to increase adherence. A study found that viral load failure was identified a median of 10.4 months earlier through viral load testing as compared to CD4 testing. CD4 testing did not identify almost half of the patients in a large cohort experiencing treatment failure.
• Gap noted in lower and middle-income countries (Tucker et al., 2014; Nelson et al., 2014); Nigeria (Rawizza et al., 2011).

7. Research is needed on what different factors affect adherence among men and women.
   
   • Gap noted based on studies from Africa, Latin America, Western Europe and North America (Ortego et al., 2012).

8. Specific additional adherence support is needed for those who initiate ARVs at CD4 counts above 250. A review of forty randomized trials found that no consensus exists on how to effectively increase adherence, particularly among those living with HIV with no symptoms. A study found that initiating ARVs at CD4 above 250 was associated with increased odds and number of treatment interruptions and increased odds of persistent increased viral load within the first three months of ARV initiation.
   
   • Gap noted, for example, in rural Uganda (Adakun et al., 2013); globally (Mills et al., 2012d).

9. Increased information on an ongoing basis is needed concerning availability of support groups for people living with HIV. A study found that people living with HIV were given one time counseling concerning the availability of support groups only when they accessed their HIV-positive serostatus and when they were critically ill, so that collecting ARVs is correlated with information of support groups and other social services.
   
   • Gap noted, for example, in South Africa (Madiba and Canti-Sigaqa, 2012).

10. Strategies are needed to address sub-optimal adherence during switch between first- and second-line ART. A study found that many patients switching from first- to second-line ART, particularly in workplace programs, were non-adherent before and after the switch.
   
   • Gap noted, for example, in South Africa (Johnston et al., 2012).

11. Interventions are needed to reduce drug resistance, particularly among those who are treatment naïve. Third line regimens may be needed in some resource limited settings. A systematic review was done on studies published on the spread of drug resistance in resource-limited settings after rollout of ART from 2001 to 2011, which reported on changes in the rate of HIV-1 drug resistance in treatment-naïve HIV-positive patients. The review found that east Africa had the highest rate of increase of drug resistance in treatment-naïve patients at 29% per year since rollout, followed by 14% in southern Africa, and 3% in west and central Africa. No specific analysis was done on gender because many studies did not include sex ratios. In total, 162 reports were included with data from 42 countries and 26,102 patients. In another study of Latin America, it was estimated that at least 6% of patients would need third line regimens within 5 years of ART initiation.
   
   • Gap noted globally (Gupta et al., 2012); and in Latin America (Cesar et al., 2014).

12. Interventions are needed to enhance counseling to successfully prepare patients for lifelong therapy. Studies have found that patients were not well prepared for life-long therapy; that adherence rates decreased over time and hospital costs increased for those who were less adherent. A study found that patients believed that ART killed other patients, not understanding that initiating ART at high viral loads and low CD4 counts reduces the likelihood of survival.
13. **Interventions are needed to address the adherence of patients who fast as part of religious practice.** A study found that fasting observed by HIV-positive patients (e.g., Ramadan) did not have a significant effect on adherence, but patients did change when they took their ARVs (Weaver et al., 2014). Another study reported that fasting was a major reason for patients to be non-adherent and to be lost to follow-up (Bezabhe et al., 2014). Counseling should include discussion of fasting when appropriate, and more studies on the impact of rescheduling drug timing on adherence can better illustrate the relationship between fasting and adherence.

- Gap noted, for example, in Indonesia (Weaver et al., 2014); and Ethiopia (Bezabhe et al., 2014).
7C. **Treatment: Staying Healthy and Reducing Transmission**

Successfully treated people living with HIV have a normal life expectancy (Sabin, 2013 cited in Justice and Falutz, 2014; Maman et al. 2012a). “There are many things that people living with HIV need to stay healthy: emotional, mental, physical and some might even say spiritual support – as well as good nutrition and access to services and medication – all of which enhances life and life expectancy” (Dilmitis, 2015).

Given the results of the START study (NIH, 2015), the most important step for staying healthy and reducing transmission is provision of ART and adherence support as soon as a person living with HIV is ready to adhere to ART for the rest of his/her life. Being virally suppressed on effective ART both improves the health of the person living with HIV as well as significantly reduces the possibility of HIV transmission to any sexual partners. However, scaling up ARVS and viral load monitoring for everyone around the world who has tested HIV-positive will remain a global challenge. For people living with HIV who are not virally suppressed, sexual risk reduction is important to stay healthy by reducing exposure to sexually transmitted infections that can accelerate HIV disease progression and by reducing exposure to drug-resistant strains of the virus. It’s also an important step to reduce transmission to new HIV-negative partners (Brown and DiClemente, 2011).

**Risk Reduction is Necessary During the Acute Stage When HIV is Highly Transmissible**

Acute HIV infection, lasting weeks or months, may account for a substantial proportion of HIV-1 transmission worldwide. Acute infection is a highly infectious stage – usually lasting between 7 and 21 days – occurring immediately following HIV infection (Cohen et al., 2011b), with highly elevated transmission for up to four months following seroconversion (Powers et al., 2011). While some have argued that acute infection is only responsible for a small percent of new infections (Williams et al., 2011b), others have argued that acute infection may lead to efficient transmission chains (Delva and Abdool Karim, 2014; Cohen et al., 2012a; Powers et al., 2014). Currently no guidelines exist for prevention of forward transmission of acute infection (Corneli et al., 2014) and a randomized controlled intervention designed to slow onward transmission did not increase retention in care, although qualitative data found that people living with HIV in the intervention stated that they knew the importance of using condoms and appreciated additional counseling (Corneli et al., 2014). [See also Prevention for Women: Partner Reduction]

Studies have shown that the efficiency of HIV transmission is directly proportional to the viral load in the transmitting individual (Blaser et al., 2014), i.e., the higher the viral load, the easier it is to transmit HIV. Yet it is difficult, if not impossible, “…to quantify risks – with an
appropriate degree of accuracy – for any specific individual in the ‘real-world’” in terms of risks for HIV transmission (Gerberry and Blower, 2011: 1120).

Acute HIV infection (or seroconversion phase) progresses into a state of chronic HIV infection that can remain relatively constant for years. This period is associated with a much lower risk of transmission compared with that of acute HIV infection, but because this period can last a median duration of eight years, the cumulative risk of transmission during these eight years can be substantial (Granich et al., 2009). Best practice for the clinical management of acute HIV infection is still under investigation (Bell et al., 2010; Hogan et al., 2012), but a study of 468 people living with HIV in the United States demonstrated that ART initiation within the first four months of infection led to CD4 counts up to 900 cells/µl or more seen in 64% of those who initiated ART in the first four months of infection, and in only 34% of those that initiated ART after more than four months of infection (Le et al., 2013). Recent studies have found that early ART limits the persistence of the HIV reservoir and replication of HIV (Ananworanich, 2014).

**Stigma and Gender Norms Can Make Efforts to Reduce Transmission Difficult for Women and Men**

Non-judgmental, non-stigmatizing interventions are urgently needed for those living with HIV who are not virally suppressed to reduce HIV transmission to sexual partners (Collins et al., 2008). Interventions both within the health sector and outside the health sector, such as transforming norms, reducing violence against women, and revising laws that criminalize non-disclosure of HIV (Groves et al., 2012), need to be implemented in order to support people to live longer and healthy lives, and practice safer sexual behaviors once someone knows his/her positive serostatus. [See also Strengthening the Enabling Environment]

“Despite the gain and progress in access to treatment – an HIV-positive diagnosis is still seen by many as a death sentence” (Dilmitis, 2014: 7). Women living with HIV suffer from high rates of violence (Kendall et al., 2012; One in Nine Campaign, 2012; Osinde et al., 2011; Aryal et al., 2012) which can create challenges in accessing ART and adherence. [See also Strengthening the Enabling Environment: Addressing Violence Against Women]

Some serodiscordant couples identify fear of transmission as a primary concern in their relationships or fear the impact that disclosure will have on the HIV-negative partner (Ananworanich, 2014; Talley and Bettencourt, 2010; Chen et al., 2011; Kelley et al., 2011). Women particularly fear the reaction of male partners if they access ART and they sometimes hide their status and even their ART medication (Machera, 2009). A study in South Africa found that among 413 men living with HIV and 641 women living with HIV, stigma and discrimination was associated with non-disclosure and that non-disclosure was associated with HIV transmission risk behaviors (Simbayi et al., 2007).

“My baby’s father said that if he...(got) HIV, I would be the one to blame...he would kill me”

—Women living with HIV who did not disclose her serostatus to her sexual partner (Groves et al., 2012: 802)
“Persistent rates of nondisclosure by those diagnosed with HIV raise difficult ethical, public health and human rights questions about how to protect the medical confidentiality, health and well-being of people living with HIV on the one hand, and how to protect partners and children from HIV transmission on the other” (Bott and Obermeyer, 2013: S5). At least 63 countries have HIV-specific criminal statutes (Dilmitis, 2014) and therefore people can be prosecuted for transmitting HIV, making disclosure and adherence challenging. In some countries, women who know their status fear being sued by their partners under laws that criminalize transmission of HIV (Hsieh, 2013).

Criminalization of transmission and nondisclosure undermines rights while disserving public health, but gender issues are key to HIV disclosure (Bott and Obermeyer, 2013). [See Strengthening the Enabling Environment: Advancing Human Rights and Access to Justice for Women and Girls] Because women are tested for HIV at much higher rates than men (many countries have a policy of mandatory testing for pregnant women), any approach that blames women living with HIV for not disclosing their status will disproportionately burden women. Health care systems that are often overwhelmed do not provide appropriate psychosocial support for pregnant women who discover their HIV-positive status through this kind of testing. Where male partners have been unwilling to get tested for HIV, some women living with HIV did not feel an obligation to disclose their positive serostatus (Groves et al., 2012). Women “reflected upon the fact that men seemed unwilling to test but preferred to blame their female partners” (MacGregor and Mills, 2011: 4). In some cases, women are significantly less likely to know their partner’s status than men (McGrath et al., 2013). And one study of women living with HIV in South Africa found that consistent condom use was not correlated with disclosure to either HIV-negative or HIV-positive male partners (Onoya et al., 2011). For women living with HIV, “it is ultimately the decision of the man to either use a male condom or not,” (Onoya et al., 2011: 1218), with gender norms on sexuality key to male use of condoms. Some evaluated interventions exist regarding women’s use of female condoms in the absence of male condom use. However, " ...limited access to female condoms and substantially higher costs have limited uptake and use of female condoms” (Abdool Karim et al., 2010a: S125) thus limiting an opportunity to reduce HIV infection through a woman-initiated prevention method. [See also Strengthening the Enabling Environment and Prevention for Women: Male and Female Condom Use]

Fear of Disclosure Impacts Transmission Reduction Efforts

Disclosure is not a one-time event but a process calling for careful consideration as to whom to disclose, when and reasons for disclosing. A study in Zimbabwe of 200 women living with HIV on ART found that 96.5% disclosed to at least one person, most frequently their sister (Patel et al., 2012). Both women and men need to learn how to negotiate safe sex prior to disclosure, knowing when to disclose and how to disclose. Given that there is no global guidance on disclosing – technicalities of why, how and when to disclose is where communities of women living with HIV become essential in providing this kind of peer support. [See Adherence and Support] Women in one study noted that once they disclosed, no man had stayed with them (MacGregor and Mills, 2011). In another study in Uganda, “the need to provide for children was a particularly strong motivation for women to avoid disclosure” (Allen et al., 2011: 539), as men abandoned or abused partners who disclosed or
requested condom use. One cross sectional survey in Cameroon found that women living with HIV who were not financially dependent on their male partners were much more likely to have used condoms (Loubiere et al., 2009), suggesting the importance of a strong supportive enabling environment. [See Strengthening the Enabling Environment]

A study in South Africa found that, for men, disclosure undermined men’s sense of masculinity and that health-seeking behavior portrayed them as weak and dependent, as well as subject to control by health care providers (Mfecane, 2012). “Men believed that ‘real men’ deal with personal problems on their own, instead of asking help from other people” (Mfecane, 2012: S115). However, once on ART, men’s health and appearance improved and they felt publicly able to share their HIV-positive serostatus, which in turn won them support, approval and admiration, becoming role models for breaking the secrecy and stigma surrounding HIV (Mfecane, 2012). Other studies found that men were particularly critical of serodiscordant couple interventions, as couples counseling puts “the man on trial.” As one man put it: “It is as if you are before a court, as you know women can get authority over the man when other people are there...So your wife may ask you how the disease came about. So you have to reveal the extra affairs...” (Siu et al., 2013: 48). Couple testing must be implemented in a way that addresses gender imbalances and violent relationships. Providing sex-segregated counseling may also be effective (Jones et al., 2014).

**Safer Conception Information is Needed for Those Who Desire Pregnancy**

Among people living with HIV who are not virally suppressed, HIV transmission can occur in the attempt to become pregnant. In most low- and middle-income countries, little information is available to couples on safer conception. “In the absence of artificial insemination technologies, effectively unavailable in most low- or low-to-middle income countries, conception requires unprotected sexual intercourse; this means risk of either HIV transmission (in serodiscordant couples) or HIV super-infection (in couples where both couples are positive)” (London et al., 2008: 14). When the person living with HIV is virally suppressed, the chances of transmission are dramatically reduced [See also Safe Motherhood and Prevention of Vertical Transmission]

Among those living with HIV and not virally suppressed, superinfection can become an additional health problem. Superinfection is when a person gets infected with different strains of HIV, increasing the risk of drug resistance to ARVs. A study in Uganda found that polygamous relationships among HIV-positive partners results in multiple infections i.e., superinfection (Ssemwanga et al., 2011). One study found that among 20,220 people in the study in Uganda in a general heterosexual population, rates of superinfection were substantial (Redd et al., 2012) and another study detected superinfection among Kenyan women (Ronen et al., 2013) but found that HIV infection provides partial protection from subsequent infection, with susceptibility to superinfection possibly decreasing over time.

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“People living with HIV have feelings...and marriage is a right to everyone, whether HIV positive or not.”

—19-year-old woman in Zambia, (Mburu et al., 2013: 178)
The Relationship Between HIV and Other STIs is Complicated

Among those living with HIV who are not virally suppressed, acquiring STIs can accelerate HIV disease progression (White et al., 2006 cited in Brown and DiClemente, 2011). STIs also increase the risks of HIV transmission (Ward and Ronn, 2010 cited in Brown and DiClemente, 2011). Infectiousness is high in people living with HIV who have a concurrent STI (Brown et al., 2011a). Women living with HIV have higher rates of the STI Trichomonas vaginalis (TV), the second most common STI worldwide, with a seven-day treatment, rather than single-dose therapy, recommended (Lazenby, 2012). A study of 3,297 African serodiscordant couples with 86 linked HIV transmissions found that STIs such as Herpes Simplex Virus-2 (HSV-2), genital ulcers, Trichomonas vaginalis, vaginitis and cervicitis among those who were HIV-negative increased risk of HIV acquisition, even after adjusting for viral load of the person living with HIV (Hughes et al., 2012). The ongoing challenge of treatment for STIs continues to be diagnostic, as well as treating the right infection with the right medication at the right time (Cohen, 2012).[See Prevention for Women: Treating Sexually Transmitted Infections]

STIs in people living with HIV may be associated with a faster progression to death. A study between 2001 and 2009 with 303 women living with HIV with 1,408 person-years in Uganda and Zimbabwe found that STI symptoms were associated with faster disease progression (Morrison et al., 2011). Women living with HIV also have increased risks for certain STIs, such as genital ulcer disease, even after initiation of antiretroviral therapy; one study found an increased risk of Trichomonas vaginalis (Mavedzenge et al., 2010).

Conversely, HIV treatment can benefit certain STI outcomes. A study found that people on ARVs with syphilis are less likely to have neurosyphilis and respond better to neurosyphilis treatment (Marra et al., 2012). Among entirely or predominantly ART-naïve adults, a systematic review found that treating STIs reduced HIV viral load (Modjarrad and Vermund, 2010). Questions have been raised about whether Herpes Simplex-2 infection, in particular, enables HIV transmission, though recent observational data found no association between HIV transmission with HSV-2. Clinical trials found no effect of HSV-2 suppression on HIV acquisition and HIV transmission in HIV discordant couples (Celum et al., 2010).

Randomized evaluations of different behavioral intervention models, including clinician-initiated communication are needed (Bunnell et al., 2006b). “When discussions of ongoing STD-related risk behavior do occur, they are infrequent and often initiated at the patient’s request. At best, the lack of these discussions in HIV-related care settings is unfortunate; at worst, it indirectly contributes to escalating rates of STIs among [people living with HIV] and of new HIV acquisition among others at risk” (Hall and Marrazzo, 2007: 518).

Treatment Can be a Successful Prevention Strategy to Reduce Transmission

The HPTN 052 study has shown that early initiation of antiretroviral therapy (when CD4 counts were between 350 and 550) for the seropositive partner in a discordant relationship resulted in a 96% relative risk reduction of HIV transmission to the seronegative sexual partner (Cohen et al., 2011a). Ten year results presented at the 8th IAS Conference on HIV Pathogenesis, Treatment & Prevention Conference in July, 2015 found durable reductions in
transmission, noting “throughout our decade-long study with more than 1,600 heterosexual couples, we did not observe HIV transmission when the HIV-infected partner’s virus was stably suppressed by antiretroviral therapy” (Cohen et al., 2015; NIH news release, 2015).

WHO’s 2013 guidance recommends ART for all people living with HIV, regardless of CD4 count, who have seronegative sexual partners, while noting that advice should be given on safer sex, including condom use (WHO, 2013). But some have criticized this strategy, noting that a person living with HIV is in a discordant relationship any time they have sex with someone of unknown serostatus. Others have noted that sero-concordant couples also deserve treatment. Still others have noted “prioritizing those in stable partnerships for treatment may not be an efficient form of prevention over providing treatment to the general population without prioritization” (Delva et al., 2012).

Furthermore, a study in Kenya found that almost 40% of serodiscordant couples were unwilling to use early treatment for preventive effect (Heffron et al., 2012 cited in Mills et al., 2013). “Increasingly, there has been recognition of the need for services to work with couples, rather than just with the individual partners” (Spino et al., 2010: 4). Some have suggested that it is important to understand population dynamics through modeling. In a recent modeling exercise, sex workers in West and Central Africa were found to have the highest probability of transmission, even in settings where HIV prevalence is low and there is not a concentrated epidemic (Boily et al., 2015). However, no evaluated studies were found that reached sex workers with treatment for their own needs rather than as vectors of transmission, with the exception of one (Mountain et al., 2014). Given the new START data showing that early treatment has health benefits for the person taking ART as well as reducing the likelihood of transmission, countries will need to assess how ART will be scaled up in a way that respects individual choice, understanding and readiness to undertake life long treatment while also reducing population level transmission.

While the study by Cohen et al., 2011a shows the benefit of treatment for reduction of transmission to the HIV-negative partner, it is important to keep this study in context. Condoms as well as treatment were used to prevent transmission, with self-reported 100% condom use correlated with prevention of transmission. There are a number of hurdles in successfully utilizing treatment as a prevention approach. For example, getting all HIV-positive people to know their serostatus before they are symptomatic and while their CD4 counts are above 350 in order to access treatment will be challenging and unlikely to result in universal coverage in the near future (Over, 2011). Also of significance in the study by Cohen et al., 2011a, is that in 28% of the cases, HIV transmission occurred from another partner rather than from the HIV-positive partner on treatment (Cohen et al., 2011a), demonstrating that monogamy cannot be assumed in serodiscordant couples (Chohan et al., 2015). Population-level benefits of ART could be compromised by sub-optimal ART coverage or adherence (Cohen et al., 2012b). The effect of ART in reducing transmission through routes other than heterosexual contact is not definitively known (Cohen et al., 2013), with clinical trials underway (Cohen et al., 2012b). Data from treatment as a prevention strategy comes almost exclusively from vaginal sex with no data for risk of transmission for anal sex, whether for those who are heterosexual or who are MSM (Collins and Geffen, 2014). However, a
recent CROI abstract (Grulich et al., 2015) found no risk of transmission among virally suppressed MSM.

But much of transmission is driven by those who are not yet diagnosed with HIV, rather than those who know their sero-status but are not yet on ART (Collins and Geffen, 2014; Phillips, 2015). A study from South Africa found that “a substantial proportion of [individuals living with HIV] remained at risk of transmitting HIV even after starting ART,” (Kranzer et al., 2013: 498), with 39.2% of individuals who reported taking ART “with detectable viral load (above 1,500 copies per milliliter), which is known to be associated with a high risk of transmission” (Kranzer et al., 2013: 501). The logistical challenges, however, of getting all who have tested positive globally on ART and virally suppressed remain daunting.

The use of HIV treatment as prevention is emerging as an exciting component of scaled up AIDS programs (WHO, 2013). Additional discussion of the use of treatment as a prevention strategy can be found in Prevention for Women: Treatment as Prevention.

**Scaling Up Treatment Alone Is Insufficient as a National Prevention Strategy**

“Given the dramatic effect of ART on viral load, it is reasonable to consider using treatment of individuals [living with HIV] as a means of preventing HIV transmission” (Dieffenbach and Fauci, 2009: 2380) and recent results “…support the use of antiretroviral treatment as a part of a public health strategy to reduce the spread of HIV-1” (Cohen et al., 2011a: 12). However, treatment programming must be linked with prevention (Holmes et al., 2010b) and “an essential question is how a country’s health service could maintain antiretroviral therapy in legions of healthy patients with high CD4 cell counts mainly for prevention benefits to partners, when it is not able to initiate and maintain high levels of retention of those with low CD4 counts who need ART for survival” (Padian et al., 2011b: 275). Rapid ART scale up can exacerbate health system constraints with neglect of prevention for both those living with HIV and those who are HIV-negative (Jacobson et al., 2012). [See also Prevention for Women] Treatment as prevention requires lifelong engagement in care (McNairy et al., 2013b), with the danger that those with high viral loads will be lost to follow up and have low rates of adherence. [See Treatment: Provision and Access & Adherence and Support] Meeting the challenges of scaling up treatment for those with high viral loads will be difficult, and therefore successfully scaling up treatment for those with low viral loads may be unlikely (Mills et al., 2013).

Some researchers have expressed concerns that risk behaviors may increase “due to the feeling of safety that ART provides” (Shafer et al., 2011: 671) and increasing HIV prevention efforts both for those who are HIV-negative and for those who are HIV-positive is necessary (Shafer et al., 2011). Treatment as prevention still faces challenges due to gender norms,
multiple partnerships, and other structural and environmental factors. [See Strengthening the Enabling Environment]

The proper use of condoms remains a reliable means of enabling everyone, without knowing the serologic status of their partners, to protect themselves and others during sexual intercourse. UNAIDS also argues that reducing transmission is a “shared responsibility”, so that everyone shares the responsibility to avoid HIV (GNP+ and UNAIDS, 2011). But women often struggle to access and negotiate condom use. [See Prevention for Women: Male and Female Condom Use and Strengthening the Enabling Environment] Guidelines on promoting the health and dignity for people living with HIV with attention to gender equity are available at: (UNAIDS and GNP+, 2013). Some contend that while treatment can provide regular condom users with added safety, “condoms remain the only way to protect oneself against other STIs” (Bourdillon et al., 2008: 11). Some studies have shown that those on treatment are more likely to use condoms (Kennedy et al., 2010b) and other measures to prevent transmission and other studies, mostly from resource-rich settings (Tun et al., 2004 cited in Cohen and Gay, 2010) have shown the opposite. Treatment as a prevention strategy still requires individual action, such as continued adherence. Even in a resource-rich country like the United States, only one-quarter of people living with HIV “have successfully navigated the ART care continuum to achieve an undetectable viral load with ART” (Fauci and Marston, 2014: 496).

The WHO 2013 guidelines recommend that all those living with HIV be enrolled in care prior to ART initiation, with recommended packages including psychosocial counseling and support (WHO, 2013). Individuals need counseling on the relationship between their CD4 count and/or viral load and the risk of transmission both to sexual partners and in pregnancy in a simple, easy to understand format (Ujiji et al., 2010). [See also Meeting the Sexual and Reproductive Health Needs of Women Living with HIV and Safe Motherhood and Prevention of Vertical Transmission] Condoms can protect partners who may not be fully adherent and/or virally suppressed, as well as preventing STI acquisition. Questions remain about transmission of ART-resistant strains to partners (Anglemyer et al., 2013).

For more information on staying healthy, see http://www.avert.org/being-hiv-positive-and-healthy.htm. For additional prevention strategies see Prevention for Women; Prevention for Key Affected Populations and Prevention for Young People

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“Let me tell you where there is health, there is life. I tried very much to be single but when I couldn’t hold on any longer I got someone who was also...on medication.”

— Women living with HIV in Uganda (Mbonye et al., 2013: 8)

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7C. What Works—Treatment: Staying Healthy and Reducing Transmission

1. Viral suppression with ARV therapy can minimize the risk of HIV transmission and improve health.
2. Providing antiretroviral treatment to people living with HIV can increase HIV prevention behaviors, including condom use.

3. Providing peer support, information and skills-building support to people living with HIV can reduce unprotected sex.

7C. Evidence

1. Viral suppression with ARV therapy can minimize the risk of HIV transmission and improve health.

- A systematic review adhering to the Cochrane Group review guidelines was conducted of observational studies and randomized control trials to evaluate the rates of sexual HIV transmission between heterosexual serodiscordant couples when the HIV-positive partner had full viral suppression on ART. Of the 3 studies that met all eligibility criteria with confirmed full virologic suppression in the HIV-positive partner, the rate of transmission was 0 per 100 person-years (no seroconversions were reported). With an additional 3 studies that did not confirm full viral suppression, the rate of transmission was 0.14 per 100 person-years; however, all transmission events occurred shortly following initiation of treatment (before viral suppression could be attained), so excluding these transmission events the rate of transmission was still 0 per 100 person-years. When converted to lifetime risk of seroconversion, the upper end of the confidence interval (.0001 per 100 person-years) demonstrates a 1 in 204 to 1 in 50 chance of transmission to the infected partner over 20 to 50 additional years of life. Studies were included that provided data on sexual contact, HIV-positive partner on ART, confirmed undetectable viral load at the time of transmission, and reported seroconversions rates. Of 20,252 records originally identified, three met all the inclusion criteria. These three cohort studies were conducted on 991 heterosexual couples in Brazil, Spain and Uganda with 2,064 person-years of follow-up. Two cohort studies and one randomized control trial were also used in further analysis that met all of the inclusion criteria except the confirmed viral load at the time of transmission. The cohort studies were conducted in Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia on 4,307 couples. The randomized control trial was the HPTN 052 trial carried out on 1,763 couples in Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand, and the United States (Cohen et al., 2011a). There was a total of 8,170 person-years of follow-up in the latter 3 studies. These studies reported 4 transmission events, all of which occurred early after the initiation of ART. The study notes that, “not enough data were available to present results on transmission rates through intercourse exclusively without condoms, by type of sexual act (vaginal vs. anal), correcting for the presence of STIs, or by female-to-male or male-to-female contact,” (Loutfy et al., 2013: 3). Unprotected sexual intercourse may not result in transmission when viral suppression in the HIV-positive partner has been confirmed (Loutfy et al., 2013). (Gray II) (treatment, sex behavior, Brazil, Spain, Uganda, Botswana, Kenya, Rwanda, South Africa, Tanzania, Malawi, Zambia, Thailand, United States, Zimbabwe)

- A Cochrane review of one randomized controlled trial (Cohen et al., 2011a) and nine observational studies conducted in Botswana, Brazil, China, India, Italy, Malawi, Kenya, Rwanda, South Africa, Spain, Thailand, Uganda, the United States of America, Zambia, and Zimbabwe was conducted to determine if ART use was associated with lower risk of seroconversion in HIV-discordant couples. This review found that in couples where the infected partner (index partner) was being treated with ART, the uninfected partner had at least a 40% lower risk of acquiring HIV than in couples where the index partner was not receiving ART. The ten studies identified 2,112 episodes of HIV transmission, 1,016 among treated couples and 1,096 among untreated couples. In the observational studies, the risk for HIV seroconversion incidence in the ART-naïve group was 54 cases per 1,000 people. The risk for HIV seroconversion incidence in serodiscordant couples
where the index partner was on ART was 31 per 1,000 people. The data was also categorized into subgroups by the index partner’s initial CD4 count. When the index partner had a CD4 count of more than 350 cells/µl, there was an 88% lower risk of seroconversion among couples where the index patient was on ART. In this group, there were 247 seroconversions in the ART-naïve group and 30 in the ART group. This review demonstrates that ART can be used as a preventive measure for HIV transmission among serodiscordant couples, and that this intervention is effective at CD4 counts above 350 cells/µl (Anglemyer et al., 2013). (Gray II) (treatment, sex behavior, CD4 counts, Botswana, Brazil, China, India, Italy, Malawi, Kenya, Rwanda, South Africa, Spain, Thailand, Uganda, the United States of America, Zambia, and Zimbabwe)

• A randomized trial of 1,763 couples in nine countries – Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand and the United States - in which one partner was HIV-1-positive and the other was HIV-negative, with 50% of partners were men living with HIV, found that early initiation of antiretroviral therapy at CD4 counts between 350 and 550 in 886 couples resulted in a 96% relative risk reduction of HIV transmission to the HIV-negative sexual partner as compared to initiation of antiretroviral therapy at CD4 counts at 250 or less in 877 couples. Of the 39 HIV transmissions, 28 were virologically linked to the infected partner. Of the 28 linked transmissions, only one occurred in the early therapy group, for an incidence rate of 0.1 per 100 person years in the early initiation group compared to an incidence rate of 0.9 per 100 person years in the later initiation group. The single HIV transmission event in the early treatment group was ascribed to transmission before HIV suppression was possible (Cohen et al., 2012b). Of the 28 HIV-positive participants who had linked transmission to a partner, 17 (61%) had a CD4 count of more than 350 cells per cubic millimeter at the study visit before the detection of linked HIV transmission. All linked transmissions in the delayed therapy group occurred while the HIV-positive participant was not receiving antiretroviral therapy. There was a relative reduction of 89% in the total number of HIV transmissions resulting from the early initiation of antiretroviral therapy, regardless of viral linkage with the infected partner. Women living with HIV were the source of infection in 18 of 27 (67%) linked transmissions in the delayed therapy group and a man was the source of the single transmission in the early therapy group. HIV-1 uninfected partners were encouraged to return for all visits together for counseling on risk reduction, condom use, and treatment of STIs. Self-reported 100% condom use at baseline was associated with a reduced risk of HIV transmission. Of the couples, 97% were heterosexual and 94% were married. At enrollment, 1,291 of the HIV-positive (73%) reported having had at least one sexual encounter during the previous weekend and 5% had unprotected sex, with a similar profile for the HIV-negative partner. Partners who seroconverted to HIV-positive were released from the study and referred for care. Any woman who was pregnant at enrollment was provided antiretroviral therapy appropriate for use during pregnancy at the start of the second trimester and women in the delayed-therapy group discontinued antiretroviral therapy at delivery or when breastfeeding ended. Twelve new HIV-negative partners who met study criteria for inclusion were enrolled with an HIV-positive partner after the original partner was released from the study (Cohen et al., 2011a). (Gray II) (treatment, sex behavior, serodiscordant, CD4 counts, Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand, United States)

• A study done utilizing behavioral data from the continuing Temprano-ANRS12136 randomized, controlled trial in Côte d’Ivoire compared the sexual behaviors of patients who received early ART as opposed to standard ART. By accounting for sexual behavior and viral loads, the study authors did calculate that the protective effect of early ART was 89% for sexually active people, which “was mainly attributable to difference in viral loads between patients receiving early versus standard ART,” (Jean et al., 2014: 435). The study found that the early ART patients reported slightly less risky sex in the past month; however, the difference was not statistically significant. So although the sexual behaviors between the standard and early ART groups was similar, ART significantly reduced the chance of transmission at each sexual encounter. HIV-positive adults were enrolled in this trial from 2008 to 2012 if they had a CD4 count of less than 800 cells/µl but did not satisfy any criteria for initiating ART. Participants were randomly assigned to initiate ART
A prospective longitudinal study was conducted in Yunnan province in China from 2009 to 2011 to assess the efficiency of China’s current HIV treatment program to prevent new HIV infections among discordant couples in rural China. In total, 813 couples were followed for an average of 1.4 person-years. The 288 couples that were lost to follow-up had a greater proportion of HIV-positive partners that were not receiving antiretroviral therapy. Routine ART was prescribed according to China’s national guidelines (CD4 count less than 350 cells/µl). During the study, the couples were classified as ART-experienced or ART-naïve. The HIV-positive partners who started ART before the beginning of the study and those who had started ART before the midpoint of the follow-up period were classified as ART-experienced. The remaining couples were classified as ART-naïve. Each partner was interviewed at baseline and at the follow-up visit. Samples were taken of each partner’s plasma at each visit to test for HIV, syphilis, herpes, CD4 count, and viral load.
couples where the HIV-positive partner is not on ART. The population on ART had a seroconversion rate of 0.8 per 100 person-years, a 66% reduction from the 2.4 per 100 person-years in the ART-naïve population (He et al., 2013). (Gray IIIa) (treatment, viral load, sex behavior, China)

- A retrospective cohort study in China from 2003 to 2011 was conducted to measure the effects of ART on transmission of HIV in serodiscordant couples. The ART-naïve cohort had a rate of transmission of 2.6 per 100 person-years and the ART-treated cohort had a rate of transmission of 1.3 per 100 person-years, demonstrating a 26% relative risk reduction in HIV transmission. ART was initiated in all HIV-positive individuals who met Chinese treatment criteria (when CD4 count dropped below 200 cells/µl until 2008, when guidelines changed to CD4 count dropping below 350 cells/µl). Repeat tests for HIV for HIV-negative partners and CD4 counts for HIV-positive partners were recommended every 6 months. Couples were taken from the databases and categorized as the treatment-naïve cohort or the treatment cohort. From the databases, 24,057 couples were included in the treatment cohort and 14,805 couples were included in the treatment-naïve cohort. A total of 1,631 seroconversions were recorded from 2003 to 2011. Treated patients generally had the same demographic characteristics as treatment-naïve patients; however, treated patients were on average older, were predominantly infected through blood or plasma transfusion, and had a longer follow-up time. Treatment-naïve patients were predominantly infected through sexual contact. Treatment was the most protective in the first year of follow-up, but not in subsequent years. Treatment was significantly protective when the HIV-positive partner had been infected through transfusion or heterosexual intercourse, but was not significantly protective when they had been infected through male homosexual sexual contact or by injecting drugs. The study also found that women were more likely than men to transmit HIV to their partner (Jia et al., 2013). (Gray IIIa) (treatment, sex behavior, prevention, China)

- A review of publications from 1996 to 2009 with 11 cohorts reporting on 5,021 heterosexual couples and 461 HIV transmission events found that studies of heterosexual discordant couples observed no transmission in patients treated with ART and with viral load below 400 copies/ml but data were compatible with one transmission per 79 person-years. In ten studies with HIV-positive people not receiving antiretroviral therapy with 9,998 person years of follow-up, the overall HIV transmission rate, irrespective of viral load category and sexually transmitted diseases, was 5.64 per 100 person years. The largest number of serodiscordant couples was reported in five studies from Sub-Saharan Africa. “There was insufficient data to allow estimation of summary rates of transmission through sexual intercourse without condoms, or to separate female-male and male-female transmission” (Attia et al., 2009: 1399). “This systematic review did not identify any study from which the risk of HIV transmission per act of unprotected sexual intercourse among persons with suppressed viremia following ART could be quantified directly. The available studies found no episodes of HIV transmission in discordant heterosexual couples If the HIV-infected partner was treated with ART and had a viral load below 400 copies/ml...The comparison of overall rates in patients on ART and not on ART nevertheless indicated that heterosexual transmission was reduced by 92%” (Attia et al., 2009: 1401). (Gray IIIa) (treatment, sex behavior, Sub-Saharan Africa)

- An analysis of data from 463 patients (70% women) in rural Uganda on ART in a government-run clinic over 3.5 years of observation and 5,239 study visits showed that although detectable viremia and/or sexual transmission risk behavior occurred in over half of patients, ART reduced periods of HIV transmission risk by over 90% over six years of observation time. Though over half of the 463 patients had episodic detectable viremia or reported sexual transmission risk behavior, less than 5% ever experienced them simultaneously. One in three reported at least one episode of sexual transmission risk during a median of 3.5 years of observation time. Lower CD4 count, stigma, low household assets and younger age were associated with HIV transmission risk (Siedner et al., 2014). (Gray IIIb) (treatment, viral load, Uganda)
Using data collected at population-wide annual serological and behavioral surveys in Uganda between 1989 and 2007, no transmissions occurred in the 29 couples where the person living with HIV was on ART during 872 person years. HIV status of both partners was known in 2,465 couples and of these, 259 were HIV serodiscordant. Of the 259 serodiscordant couples, 62 converted to HIV. Higher viral load independently associated with HIV seroconversion (Biraro et al., 2013).

A review of data from a population based prospective cohort of 16,667 individuals in South Africa who were HIV negative in 2004 and were followed until 2011 found that an HIV-negative person living in a community where 30% to 40% of those living with HIV were on ART was 38% less likely to acquire HIV than an HIV-negative person living in a community where ART coverage was less than 10% after ruling out confounding factors. From 2004 to 2011, 1,413 HIV-negative people seroconverted, with a 1% increase in ART associated with a 1.4% decline in risk of acquisition of new HIV infection. Controlling for other factors, an HIV-uninfected individual was 2.2 times as likely to acquire HIV in a community where HIV prevalence was under 25% compared to under 10%. Controlling for reported condom use did not affect the strong relationship between ART coverage and the risk of HIV acquisition. ART was delivered in 17 community-based clinics by nurses and ART counselors for those with CD4 under 200 until 2011; and from 2011, to those with CD4 under 350 in the context of a “successful, but imperfect, real-world ART program” (Tanser et al., 2013: 970). All those who tested HIV-positive were included, whether they accessed ART or not. Within a five-year period, 80% were tested for HIV. The group of 16,667 repeat testers constituted 75% of the population who were HIV-negative at the first observation. There was little correlation between community level HIV prevalence and ART coverage (Tanser et al., 2013).

A study of 3,297 serodiscordant African couples found that each 10-fold increase in viral load was associated with a 2.9 fold increase in per-act transmission risk. The study found no viral load above which infectivity did not continue to increase (Hughes et al., 2012).

2. Providing antiretroviral treatment to people living with HIV can increase HIV prevention behaviors, including condom use.

A 2007 review of evidence for the impact of ART on sexual behavior in developing countries found three relevant studies conducted in Africa—one in Côte d’Ivoire and two in Uganda. In each study, condom use at last sexual intercourse was significantly higher among ART patients compared to non-ART patients. In the Côte d’Ivoire study of 711 patients, condom use at last sex was 80 percent for ART patients versus 59 percent for non-patients, regardless of partnership type (Moatti et al., 2003). Bateganya et al. on reported that of 926 participants in Uganda, of whom 164 received ART. Condom use was higher among ART patients: 71 percent used condom use at last sex with a spouse for ART patients, versus 47 percent for non-ART patients (Bateganya et al., 2005). Among study participants receiving weekly home-based ART delivery and individual counseling in Uganda, Bunnell et al. found that of 723 patients, with 354 ART-naïve patients and 369 ART-experienced patients, condom use at last sex increased from 59 to 82 percent among ART-experienced patients with uninfected partners or with partners they did not previously know, and from 58 to 74 percent among ART-experienced patients with HIV-positive partners (Bunnell et al., 2006a). In individual counseling sessions, participants developed personal sexual behavior plans. Free condoms were provided. The available evidence indicates a significant reduction in risk.
behavior associated with ART in developing countries. However, there are few existing studies and the rigor of these studies is weak (Kennedy et al., 2007). (Gray IIIa) (treatment, risk behavior, Côte d'Ivoire, Uganda)

- A study of 1,163 sexually active people in South Africa living with HIV found that ART was consistently associated with decreased sexual risk behaviors, as well as reporting a partner who was HIV negative or of unknown sero-status. Participants on ART were consistently less likely to engage in sexual risk behaviors, which held even after adjusting for HIV disease progression and time in care. Those who were on ART were less likely to have a sexual partner who was HIV-negative or of unknown serostatus (Venkatesh et al., 2012). (Gray IIIb) (treatment, sex behavior, South Africa)

- A cross-sectional study conducted in 2005 found that consistent condom use among sexually active people living with HIV in Uganda was correlated with being on ART for more than one year. The study analyzed data on 269 sexually active ART-experienced individuals (95 males and 174 females, with 71% of men and 61% of women reporting consistent condom use after initiating ART. Of the men, 83% and of the women, 89% believed that ART did not reduce HIV transmission. Those men and women desiring to have children were significantly less likely to use condoms. Results suggest that people living with HIV wanted to protect their HIV-negative partners from acquiring HIV and wanted to protect HIV positive partners from re-infection. Consistent condom use was less likely among those who were married, possibly due to lack of control by women over sexual decision-making within marriage, as well as a lack of understanding of the concept of serodiscordance (Ayiga, 2012). (Gray IIIb) (treatment, condoms, sex behavior, Uganda)

- An observational cohort study from 2004 to 2009 of 250 HIV-1 serodiscordant couples in Uganda found that couples reported more consistent condom use during ART use, but with no significant difference in the number of sexual partners. Of the 250 couples, 32 HIV-positive partners were started on ART (Reynolds et al., 2011). (Gray IIIb) (treatment, risk behavior, condom use, Uganda)

- A study of 559 HIV-positive people in Uganda, 386 women, found that ART initiation was correlated with increased condom use. Among those sexually active, unprotected sex decreased during the first 12 months from 53% to 15% and stabilized at 11.5% over the next two years. However, believing that ART reduced the risk of HIV transmission was independently associated with higher prevalence of unprotected sex. Although women receiving ART were less sexually active than men, those women who had sex were three times more likely to report unprotected sex in multivariate analysis, possibly due to lack of availability of female condoms. Only male condoms were available at the clinic and required partner consent (Wandera et al., 2011). (Gray IIIb) (treatment, condom use, risk behavior, Uganda)

- A study in South Africa with 1,544 men and 4,719 women from 2003 to 2010 from 19,703 clinics found that condom use increased following ART initiation. Of 13,604 visits at which sexual activity was reported, participants reported unprotected sex at 1,968 pre-ART visits, or 20.6% of all visits, compared to 346 post-ART visits, or 9.9% of all visits. Both men and women reported a higher frequency of unprotected sex prior to ART initiation. Unprotected sex decreased after ART initiation, with a greater decrease for men than for women. In addition, the likelihood of having more than one sex partner decreased after ART initiation ad this decrease was greater for women than for men. Decreased risk behavior was independent of CD4 cell count. (Venkatesh et al., 2010). (Gray IIIb) (treatment, condom use, HAART, risk behavior, South Africa)

- Data analyzed from a prospective cohort of 3,381 participants living with HIV in a serodiscordant relationship in Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia found the proportion of visits at which reports of sex was unprotected by condoms decreased from 6.2% prior to ART initiation to 3.7% following ART initiation, with no difference between men
and women, a significant difference. The number of sex acts per month did not differ prior to and following ART initiation (Donnell et al., 2010). (Gray IIIb) (treatment, risk behavior, Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia)

- A prospective cohort in Uganda of HIV-negative household members of HIV-positive patients on ART receiving home-based care found that risky sex decreased among HIV-negative adult household members. The study of 182 men and 273 women found that inconsistent condom use decreased from 29% at baseline to 15% at 24 months (Bechange et al., 2010). (Gray IIIb) (treatment, condom use, Uganda)

- An analysis of survey data from a cross-sectional study with 85 HIV-positive women from Uganda; 50 HIV-positive women in South Africa; and 44 HIV-positive women in Brazil found that HAART users were significantly (3.6 times) more likely to use condoms. Of the 179 HIV-positive women, 83 women reporting recent sexual intercourse, with 63% using condoms and 76% using contraceptive methods. Of the 179 HIV-positive women, 65% reported currently using HAART (Kaida et al., 2008). (Gray IV) (treatment, condom use, contraception, Uganda, South Africa, Brazil)

3. Providing peer support, information and skills-building support to people living with HIV can reduce unprotected sex.

- A meta-analysis of randomized controlled trials of prevention interventions that measured unprotected vaginal or anal intercourse, and included skills training, group strategies for practicing safer sex, case management, positive consequences of safer sex, peer-led discussion groups, motivational enhancement, peer mentoring, and trauma coping among 11,286 people living with HIV by 2012 (21 studies) found a lower likelihood of unprotected vaginal and anal intercourse were observed in intervention arms compared to comparison arms. All studies took place in the United States. The short-term efficacy of interventions with under 10 months of follow up were statistically significant in reducing unprotected vaginal and anal intercourse. Group based interventions were more effective than individual based interventions. The effect of the intervention after ten months of follow up was not significant, suggesting that booster interventions are needed (Yin et al., 2014). (Gray I) (treatment, sex behavior, counseling, United States)

- A cluster randomized trial of 1,891 people living with HIV on ART found that those who received a brief intervention using motivational interviewing during routine clinic care in publicly funded HIV clinical care sites in South Africa reported significantly greater reductions over a four week period in penile-vaginal or penile-anoal sex without a condom with any partner regardless of serostatus. Those in the intervention group reported a 72% reduction in sexual acts without condom use from the start of the intervention until 18 months later; those in the standard of care reported 45% reduction in sexual acts without condom use, a significant difference. Those in the intervention group received one-on-one counseling with trained lay counselors assessing sexual risk behaviors; barriers to safer sex; and decided on an achievable goal. Lay counselors who were already employed in the clinics received a five-day training. The study took place from 2008 to 2010 in eight clinics randomized to the intervention and eight clinics to standard of care. Those in the intervention arm received an average of five counseling contacts, with significant increased condom use with sexual partners, regardless of their partners’ serostatus, at 6, 12, and 18-month assessments. However, no differences were found in the control and interventions groups by new sexually transmitted infections, who may or may not have received effective STI treatment. In addition, 24.6% in the standard of care group and 28.1% in the intervention group were “currently trying to have a baby” (Fisher et al., 2014: 17). (Gray II) (treatment, counseling, condom use, South Africa)

- A randomized trial of 48 women living with HIV in Nigeria who completed a six-month follow up assessment found that motivational group support resulted in significantly higher levels of condom
use in the last three months, with 84.6% in the intervention group reporting condom use compared to 43.8% of those in the standard of care. Among the intervention group, 93% reported never missing any medication compared to 40% of the standard of care group. Among the intervention group, 92% of women reported not having sex because condoms were not available compared to 29.4% in the standard of care group. Facilitators received a 24-hour training. Group support focused on topics such as negotiation skills and disclosure (Holstad et al., 2012). (Gray IIIa) (treatment, counseling, support, Nigeria)

- An intervention with 216 couples in Zambia that addressed condom use within serodiscordant relationships to avert transmission of HIV; and within seroconcordant relationships to avert transmission of ART-resistance increased condom use over time, decreased intimate partner violence and increased positive communication. Group sessions of eight to ten participants discussed conflict resolution, sexual negotiation, effective communication and ARV adherence, as well as relaxation to respond to stress, and role-playing negotiation. All sessions were conducted separately for men and women but participants were given “couples homework” between sessions. Disclosure of serostatus was not required as part of group sessions, and group sessions included both HIV-positive and negative participants. Couples had at least six months of partnerships. Individual sessions were conducted by facilitators and provided counseling on risk reduction strategies. Condom use increased over time for both men and women who participated in group sessions, but only for men, not for women, who participated in individual sessions. Men used more positive communication strategies over time. Reports of violence decreased at 6 and 12 month follow up sessions, but only for women in individual sessions not in group sessions. Reports of use of violence predicted less male condom use. Partners who were more willing to use methods that prevented STDs reported a higher rate of condom use. Individuals who used more negative communication reported lower rates of condom use. Both individual and couples sessions increased condom use and communication between partners (Jones et al., 2014). (Gay IIIb) (treatment, counseling, condom use, Zambia)

- A study in Ethiopia in 2010 with 454 people living with HIV, 224 ART-naïve and 230 ART-experienced found that those who were a member of an association of people living with HIV had a 40% lower risk of using condoms inconsistently in both ART experienced and ART naïve groups. In addition, knowledge that HIV transmission can occur while on ART also was correlated with higher likelihood of condom use (Yalew et al., 2012). (Gray IIIb) (treatment, condom use, Ethiopia)

- A qualitative study of 18 women with four focus groups from 10 different support groups led by para-professionals in Rwanda found that the support group empowered women to disclose their serostatus to their children, created a sense of community, gave them motivation to live, improved their self-esteem and independence, and insisting on condom use (aided by the trauma counselor) and/or choose not to have a sexual partner (Walstrom et al., 2013). (Gray V) (treatment, support groups, Rwanda)

- A study based on interviews with 21 male and 20 female clients in Uganda receiving ARVs from TASO in Uganda as well as ongoing counseling, found that concerns about reinfection, focusing on providing for themselves, their families and their children reduced multiple partnerships and increased condom use, but some women faced violence when requesting condom use (Allen et al., 2011). (Gray V) (treatment, counseling, sexual partners, violence, Uganda)

7C. Gaps in Programming—Treatment: Staying Healthy and Reducing Transmission
1. Intensified efforts are needed to increase male and female condom access and use and reduce multiple partnerships by people who know their HIV-positive status and are not virally suppressed, including young people.

2. Providers and people living with HIV need accurate information on how HIV is transmitted and how most effectively to reduce the likelihood of transmission among serodiscordant couples (or between those who do not know their sero-status), including those who wish to become pregnant – for their own health and that of their future children.

3. Increased detection of acute infection, along with immediate, effective counseling and support is needed.

4. Research and interventions are needed to better to support people living with HIV with disclosure and reduce stigma so they can adhere to ART and can continue to have a healthy and safer sex life.

5. Additional evidence- and rights-based interventions are needed for couples counseling in sero-discordant relationships; counseling that clearly explains serodiscordance and can identify women at risk of violence and make appropriate links to other services.

6. Further efforts are needed to identify an optimal strategy for safe partner notification.

7. Interventions are needed to mitigate adverse events such as stigma or violence when women disclose their serostatus to their partners.

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1. **Intensified efforts are needed to increase male and female condom use and reduce multiple partnerships by people who know their HIV-positive status and are not virally suppressed, including young people.** Studies found that consistent condom use between discordant couples (or with partners whose serostatus was unknown) was low and, among those on treatment, decreased over time. Lack of condom use was associated with fear of disclosure. People living with HIV as well as couples also believed that treatment with antiretroviral therapy meant that they were either cured of HIV or could no longer transmit the virus and were less likely to disclose their positive serostatus. In some studies, men are more likely to report condom use than women, "given the limited control that women have over the use of the male condom" (Walusaga et al., 2012: 698). Particular attention is also needed to provide condoms to men living with HIV who frequent sex workers, as well as for sex workers themselves to protect themselves (Paz-Bailey et al., 2012). [See Prevention for Key Affected Populations: Female Sex Workers]

- Gap noted, for example, in a Cochrane review (Carvalho et al., 2011); Honduras (Paz-Bailey et al., 2012); El Salvador (Jacobson et al., 2012); Nigeria (Omunakwe et al., 2014; Amoran and Ladi-Akinyemi, 2012); Russia (Davidson et al., 2012); South Africa (Onoya et al., 2011); Kenya (Ragnarsson et al., 2011); India (Oyomopito et al., 2010; Chakrapani et al., 2010); Ukraine (Saxton et al., 2010); Mozambique (De Walque et al., 2012; Pearson et al., 2011); Vietnam (Thanh et al., 2009b); Zimbabwe (McClellan et al., 2010); Cameroon (Loubiere et al., 2009); Peru (Juarez-Vilchez and Pozo, 2010); China (Mao et al., 2010); Côte d'Ivoire (Protopopescu et al., 2010); Uganda (Walusaga et al., 2012; Beyeza-Kashesya et al., 2011; Birungi et al., 2009a; Birungi et al., 2009b; Birungi et al., 2009c; Bunnell et al., 2005); Thailand (Tunthanathip et al., 2009); Ethiopia (Deribe et al., 2008); Zambia and Rwanda (Dunkle et al., 2008); Cameroon, Kenya, Tanzania, Burkina Faso and Ghana (De Walque, 2007).
2. Providers and those living with HIV need accurate information on how HIV is transmitted and how most effectively to reduce the likelihood of transmission among serodiscordant couples (or between those who do not know their sero-status), including those who wish to become pregnant – for their own health and that of their future children. [See also Safe Motherhood and Prevention of Vertical Transmission: Preconception] Studies found that both providers and HIV serodiscordant couples were misinformed as to what factors increase the likelihood of HIV transmission.

   • Gap noted, for example in Uganda (Beyeza-Kashesya et al., 2009); Rwanda and Zambia (Kelley et al., 2011); South Africa (Matthews et al., 2011).

3. Increased detection of acute infection, along with immediate, effective counseling and support is needed. A trial is underway in Botswana to identify those with high viral loads to initiate treatment (Novitsky et al., 2010 cited in Delva and Abdool Karim, 2014).

   • Gap noted, for example, globally (Cohen et al., 2011b; Miller et al., 2010; Hull and Montaner, 2011; Mlisana et al., 2013; McNairy and El-Sadr, 2014); in USA (Kelly et al., 2009); Malawi and South Africa (Pettifor et al., 2011); Mozambique (Serna-Bolea et al., 2010).

4. Research and interventions are needed to better to support people living with HIV with disclosure and reduce stigma so they can adhere to ART and can continue to have a healthy and safer sex life. In-depth interviews with patients in South Africa who were acutely infected found that patients did not retain the information that they are very likely to transmit HIV and that condom use was particularly important, but were focused on identifying who transmitted HIV to them. In addition, patients were still in shock on learning of their HIV status and did not understand how they could be HIV-positive if they tested negative with a rapid HIV test (Wolpaw et al., 2014). Women who were acutely infected in South Africa faced profound “challenges, immediately after HIV diagnosis” (Tomita et al., 2014b: 1118). Focus groups of women living with HIV found that women were concerned that their access to lifelong treatment when becoming pregnant may discourage their men from condom use, as men know that treatment can decrease the risk of transmission.

   • Gap noted, for example, in South Africa (Groves et al., 2012); Uganda (Mbonye et al., 2013); Honduras (Paz-Bailey et al., 2012); Malawi and Uganda (Hsieh, 2013).

5. Additional evidence- and rights-based interventions are needed for couples counseling in sero-discordant relationships; counseling that clearly explains serodiscordance and can identify women at risk of violence and make appropriate links to other services. While WHO issued recommendations on couples testing and counseling (WHO, 2012g), more evidence-based interventions are needed for counseling for couples in sero-discordant relationships. These interventions may need to differ by sex, as in one study, women living with HIV were likely to report an HIV-negative or unknown serostatus partner and men living with HIV were more likely to report multiple sexual partners.

   • Gap noted, for example, in South Africa (Venkatesh et al., 2012).

6. Further efforts are needed to identify an optimal strategy for safe partner notification. A Cochrane review, including studies from developing countries, found insufficient evidence to determine how partners could or should be notified of their partners HIV status, either by the patient or the provider.
7. **Interventions are needed to mitigate adverse events such as stigma or violence when women disclose their serostatus to their partners.** [See also Strengthening the Enabling Environment] A study found that women who disclosed their positive serostatus to their sexual partners feared abandonment; fear that the relationship would end; and fear of stigma. Of women who disclosed their positive serostatus to their partner, 59.3% experienced a negative reaction, such as violence, break-up of the relationship, being blamed, stigma and abandonment.

- Gap noted, for example, in **Uganda** (Mbonye et al., 2013); **Zambia** (Jones et al., 2014); **South Africa** (Groves et al., 2012); **Ethiopia** (Gari et al., 2010); **globally** (Gregson and Garnett, 2010).
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