# Chapter 10. Preventing, Detecting and Treating Critical Co-Infections

Certain infections can be significantly more severe and lead to early death for people living with HIV. Tuberculosis (TB) has become the leading cause of death for those living with HIV. Malaria can have serious impacts on pregnant women. Co-infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV), if untreated, increases the risk of non-liver and liver-related illness and death in people living with HIV. A systematic review of 18 studies found that treating co-infections such as TB, malaria, helminthes and STIs reduced viral load, even among populations that were entirely or predominantly ART naïve (Modjarrad and Vermund, 2010). Tuberculosis, malaria and hepatitis, when present as co-infections with HIV, warrant further discussion regarding their prevention, detection and treatment. Sexually transmitted infections are discussed in *Prevention for Women: Treating Sexually Transmitted Infections* and in *Meeting the Sexual and Reproductive Needs of Women Living with HIV*. Helminth infections are outside the scope of this review.

A. Tuberculosis
B. Malaria
C. Hepatitis

## *What Works in Preventing, Detecting and Treating Critical Co-Infections*

### 10A. *Preventing, Detecting and Treating Critical Co-Infections:* Tuberculosis

> *"TB continues to be the leading cause of death among people living with HIV" (UNAIDS, 2009e: 3).*

Tuberculosis is the leading cause of death among people with HIV globally, accounting for almost 25% of all HIV deaths in 2008 (WHO, 2009i). The risk of acquiring TB is 21–34 times greater among people living with HIV than in the general population. In 2010, of 8.8 million incident TB cases worldwide, 1.1 million were among people living with HIV, with an estimated 350,000 deaths (WHO, 2011f). More than half a million women of child-bearing age die from TB each year (STOP TB Partnership, 2011).

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In some countries in sub-Saharan Africa, up to 70% of people living with TB are also living with HIV (WHO et al., 2012d). Sub-Saharan Africa continues to account for the majority of people living with HIV and TB in the world with about 82% of the estimated total people living with HIV and TB in 2010. South East Asia, mainly India, accounts for 13% of the remaining cases. However, in 2010, only 34% of TB patients globally knew their HIV status and only 5% of people living with HIV were screened for TB (WHO, 2011f).

*HIV Infection Fuels TB Epidemics*

When an HIV epidemic is in an expansive phase, HIV and TB co-infection rates have rapidly increased. For example, HIV seroprevalence among TB cases in Chiang Mai, Thailand increased from 5% in 1989 to 40% in 1992, along with the rapidly growing HIV epidemic (Payanandana et al., 1995 cited in Raviglione et al., 1996; Kharsany et al. 2006). "The risk of TB increases with advancing immunodeficiency, so as the HIV epidemic in a community matures, the burden of HIV-associated TB may be expected to increase, even after the prevalence of HIV infection has stabilized" (Lawn et al., 2006: 1046).

*TB Is a Serious Risk for Those Living with HIV*

Not everyone exposed to TB has active disease. A person with latent TB infection, or LTBI, has been infected with the TB bacillus but has an immune system sufficiently intact to control the infection and will not permit the bacillus to cause disease. A person with LTBI is *not* ill and is *not* infectious. TB becomes a much more serious problem for someone with HIV. When a person infected with the TB bacillus cannot control the infection because of a compromised immune system, the bacillus is able to multiply so that there are millions of TB bacilli that then cause disease. A person with active TB disease becomes sick and is considered infectious to others.

Individuals living with HIV are up to 50% more likely to develop TB in than those not living with HIV (WHO et al., 2012d). Among individuals with latent TB, HIV is the strongest known risk factor for progressing to active TB (CDC, 2012). In some sub-Saharan African countries, 70% of patients infected with TB also have HIV. Without proper treatment, nearly 90% of those living with HIV die within months of contracting TB and nearly 25% of deaths among people living with HIV are due to TB (WHO et al., 2012d). People whose immune systems have deteriorated due to advanced HIV disease are at greatly increased risk of developing active TB disease from a previously contained latent infection. Some immunocompromised people may not be able to contain a new TB infection and will immediately progress to active disease upon exposure to TB. Additionally people with HIV are more likely to develop extra-pulmonary TB (TB outside of the lungs) that may involve multiple organs and is harder to diagnose (Zvandasara et al., 2006).

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Incidence of TB has fallen or stabilized in many developed countries in the last thirty years; however "not in Eastern Europe or countries of the former Soviet Union" (Altice et al., 2010: 374) where TB has emerged as a leading cause of morbidity and mortality in HIV-infected drug users.

*Progress in TB Testing and Treatment is Being Made*

Globally, HIV testing among TB patients has made progress with the number of notified TB cases with a known HIV status increasing from 16% in 2007 to 34% in 2010. In Africa, testing increased from 37% in 2007 to 59% in 2010 among notified TB cases (WHO, 2011f).

A study in Cameroon found that some patients preferred to treat their immediately life-threatening TB before testing for HIV to "become physically/mentally strong before facing the challenges of testing for HIV" (Njozing et al., 2010: 30). However, treating HIV at earlier stages, as now recommended by WHO, may reduce the incidence of TB/HIV co-infection (Gopal and van der Horst, 2010). Preliminary results from a recent study found that a household HIV counseling intervention reduced TB prevalence by 22% and increased HIV testing (Ayles et al., 2012), but further details on the intervention are awaited.

New technological advances, such as the GeneXpert MTB/RIF assay, may also contribute to progress with new diagnostics on the horizon. Although Xpert may miss some active TB cases among those with advanced immunosuppression (Theron et al., 2011 cited in Grant et al., 2011) and costs may be a concern (Grant et al., 2011; Abimbola et al., 2012 cited in Smart, 2012b), the technology is an improvement. Prior to the development of Xpert, the most widely used test to detect TB – smear microscopy – was 125 years old and routinely missed half of all cases (Small and Pai, 2010). Countries will, however, continue to require adequate laboratory services for microscopy and culture to detect drug resistance (WHO, 2011f).

*Treatment Adherence Is Critical to Curing TB and Reducing the Spread of Drug-Resistant Strains*

Adherence to the full course of treatment—six months for first-line treatment—is essential to cure TB and avert the development of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). MDR-TB (where the disease has developed resistance to two of the first-line TB drugs, isoniazid and rifampicin, requires between 18–24 months of often complicated and expensive combination therapy. Of the 12 million estimated prevalent TB cases in 2010, it is estimated that 650,000 cases were multi-drug resistant TB. Treatment success varies by country, ranging from 23% in South Africa to 74% in Kazakhstan (WHO, 2011f). XDR-TB is resistant to first and second-line drugs and significant efforts are often needed to identify a therapeutic regimen that works and to manage side effects. By the end of 2011, 77 countries had reported at least



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one case of XDR-TB. Globally, an estimated 9% of MDR-TB cases have XDR-TB (WHO, 2012e). WHO updated the tuberculosis treatment guidelines in 2010, confirming its prior recommendation of drug susceptibility testing (DST) at the start of all therapy for previously treated patients in order to find and treat MDR-TB; it also addresses the prevention of *acquired* MDR-TB, where new TB patients have isoniazid-resistant TB when they begin treatment (WHO, 2010b).

For people who are living with HIV, MDR-TB or XDR-TB co-infection results in high levels of early mortality. A retrospective observational study in Tugela Ferry, South Africa of 272 MDR-TB and 382 XDR-TB cases, of which 90% and 98% respectively were HIV co-infected, found that mortality at one year was 71% for MDR-TB and 83% for XDR-TB patients. The majority of deaths occurred within the first thirty days of sputum collection, with mortality rates worsening with greater degrees of drug resistance (Gandhi et al, 2009).

The high rate of mortality within the first thirty days is of concern considering it typically takes 6 to 8 weeks to diagnose drug-resistant TB by traditional culture and drug-susceptibility testing methods. "The majority of patients do not survive long enough to receive their drug-resistant TB diagnosis and to initiate treatment." Of note, forty-three percent of MDR-TB cases and 56% of XDR-TB cases were women (Gandhi et al, 2009: 83). However, a global review of MDR-TB did not find an association between MDR-TB and HIV, nor any statistically significant different rate of MDR-TB by sex (Zignol et al., 2011).

It is important to note that drug-resistant TB can be transmitted. "Overcrowded, poorly ventilated clinics that bring together large numbers of HIV-infected persons, some with active TB, will be a recipe for disaster" (IOM, 2005:107). Therefore in health care facilities where people with HIV and/or TB access screening, treatment and support, and where TB transmission may be most efficient, measures should be taken to reduce the risk of primary transmission of TB, both drug-resistant and susceptible. Rapid drug susceptibility testing, prompt initiation of effective TB treatment and implementation of infection control measures such as separation of TB suspects, improving patient flow and increasing ventilation may reduce the risk of TB transmission in health care settings.

*There Are Gendered Dynamics in TB Prevalence, Detection*

"Traditionally, the majority of TB cases were reported in men, but the global HIV epidemic induced major changes in TB epidemiology. The preponderance of women living with HIV (women account for up to 70% of adults living with HIV in areas were heterosexual HIV transmission is dominant) may explain why more women than men receive a diagnosis of TB in countries where HIV infections prevalence is high" (Marais, 2011: 304). "By the end of 2007, relatively more women had TB detected than men in countries with a prevalence of HIV infection >1%" (Getahun et al., 2010: S204). A study in Rwanda found that even though the majority of adult TB cases reported to the



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surveillance system were male (60%), for women with smear-positive pulmonary TB, the risk of death was twice as great as the risk among men and more women were co-infected with HIV (Uwizeye et al., 2011).

A summary of the Stop TB symposium on the needs of pregnant women and children living with TB stated there is a considerable burden of TB among women and children. In 2010, there were approximately 3.2 million new TB cases among women, with 320,000 TB deaths among HIV-negative women and about 500,000 TB deaths occurred among women living with HIV (Smart, 2012a). In South Africa, the region with the highest global HIV prevalence, women aged 15-24 have rates of TB 1.5 – 2 times greater than men of the same age, and the pattern is consistent across each of the countries in the region (Deluca et al., 2009 cited in Smart 2012a), although "there are problems reliably estimating the burden of TB disease among women, because about 30% of countries are not disaggregating cases by sex" (Smart, 2012a: 3).

In 2010, 64% of TB cases were among men compared to 36% among women (WHO, 2011f). The reasons for the higher global TB notification rates in men are not well understood and could result from a variety of biological or environmental factors such as the likelihood of producing a positive sputum sample, delays in health-seeking behavior, gendered dynamics within the family, stigma and access to care: women are less likely to produce positive sputum samples and more likely to have extra-pulmonary TB and/or be co-infected with HIV (Lawson et al., 2008; Karim et al., 2008; Sreeramareddy et al., 2008).

Preliminary data suggest that the implementation of the revised WHO case definition of smear-positive TB was associated with significant increases in case detection among women in Kenya (Ramsey et al., 2009). The revised guidance lowers the number of bacilli detected in a sample and reduces the number of reported smear-positive results from two to one required be classified as a TB case. Evidence from a Vietnamese study also suggests that women are slower to progress to smear-positive disease despite similar time from symptom onset to diagnosis as men (Thorson et al., 2007). Additionally, some studies have shown that physicians are less likely to conduct TB exams on women than men (Begun et al., 2001 cited in Theobald et al., 2006). However, a recent study from Thailand with 480 newly diagnosed TB patients of whom 86 were living with HIV, found very small differences between men and women in delaying a visit to a provider for TB, with a short median delay of 26 days (Pungrassami et al., 2010). Further research is needed to understand the role of sex in TB-HIV co-infection (Nakanjako et al., 2010).

*Co-Infection is Particularly Deadly for Women During Their Childbearing Years*

A summary of the Stop TB symposium on the needs of pregnant women and children living with TB stated that up to 11% of pregnant women living with HIV have TB and there is an increased risk of transmitting TB and HIV to infants born of mothers with



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TB/HIV co-infection (Mepham et al., 2011; Smart, 2012a). The U.K. Department for International Development (DFID) recommends integration of strategies to address TB/HIV co-infection in maternal and reproductive health services (UKAIDS, 2012). Women bear the greatest burden of HIV during their childbearing years, and similarly, the greatest burden of TB during those years as well. It is estimated that 15% of maternal deaths are among women co-infected with TB and HIV (Adhikari, 2009; Klotz et al., 2007; Mofenson and Laughton, 2007; Zwang et al., 2007; Ramogale et al., 2007; Gupta et al., 2011b). The development of TB disease is associated with a four-fold increase in AIDS-related deaths among women co-infected with TB and HIV (Lopez-Gatell et al., 2007). A study in South Africa found young women to be at particular risk. Epidemiologic changes in TB notifications and the prevalence of HIV infection from 1996 to 2004 in a peri-urban community in South Africa of 13,000 found that annual TB notification rates among adolescents increased from zero cases between 1996-1997 to 436 cases per 100,000 in 2003- 2004, with TB cases predominantly among female adolescents (Lawn et al, 2006).

The U.S. Centers for Disease Control and Prevention states that TB treatment for pregnant women should be the same as for nonpregnant women, but with special considerations for particular medications' effect on both the woman and the fetus (CDC, 2009a, http://www.aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?MenuItem=Guidelines&Search=Off&GuidelineID=211&ClassID=4). "Pregnant women on ART who have a diagnosis of active TB should have their ARV regimens adjusted as needed to accommodate their TB drugs. For women whose diagnosis includes concurrent active TB and HIV infection during pregnancy, TB therapy should be initiated immediately and ART should be initiated as soon as possible thereafter, usually according to the principles described for nonpregnant adults" (CDC, 2009a). Co-infection with TB can also require changes in ARV regimens for those living with HIV. A cohort study in Côte d'Ivoire of 2,012 adults living with HIV who started ART between 2004 and 2006 examined factors affecting changes in treatment and found that co-infection with tuberculosis, along with pregnancy and drug intolerance were the most common factors requiring drug modifications (Messou et al., 2010).

Because of the increased risk of maternal and infant mortality associated with TB and HIV co-infection during pregnancy and postpartum, there is an urgent need to implement TB screening as part of routine antenatal and postpartum care as well as treatment for latent and active TB for women (Mofenson and Laughton, 2007). Maternal and child health and HIV/AIDS prevention programs that include TB education and screening make these services more accessible to women of childbearing age. The NIH-funded IMPAACT trials network will be conducting a randomized trial, the TB Apprise Trial (IMPAACT P1078) looking at the safety and timing of isoniazid preventative therapy in pregnancy and postpartum period – to provide some additional evidence on the risks and



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benefits of isoniazid preventative therapy in pregnant women (Smart, 2012a). There is also a need for additional research on MDR-TB in pregnancy, as there are less than 100 case reports (Gupta, 2009 cited in Smart, 2012a). Very few TB control programs have "successfully carried out isoniazid preventative therapy on a large scale" (Dye, 2011: 2230), due to yearlong treatment needed as well as other issues (Dye, 2011). However, new preventive therapies are under development, requiring larger studies to assess impact (Sterling et al., 2011 cited in Dye, 2011).

For women with both HIV and TB who wish to avoid an unintended pregnancy, potential drug reactions with anti-TB therapy "can make the management of hormonal contraception more challenging," (McCall and Vicol, 2011: 196). *[See Meeting the Sexual and Reproductive Needs of Women Living with HIV]*

*Active Case Finding Is Necessary to Increase TB Detection*

Only about half of TB suspects seek out TB screening, and it is estimated that about half of these cases are misdiagnosed (Ayles, 2009). "Sputum smear microscopy, the tool for TB screening in most resource-limited settings, has low sensitivity to diagnose TB disease, especially in HIV-infected patients with advanced immunodeficiency" (Colebunders and Bastian 2003; Siddiqi et al. 2003; and Kibiki et al. 2007 as cited in Worodria et al 2010). Many of the TB control strategies like passive case finding [as opposed to active case finding where health workers actively screen people for TB symptoms] and directly observed therapy (DOT), that are used today were developed in the pre-HIV era, and "[do] not take into account the profound impact of HIV on tuberculosis incidence" (Reid et al., 2006: 485). This situation is compounded by the fact that TB is more difficult to diagnose in people with HIV-related immune suppression.

Active case finding increases TB detection, particularly in sub-Saharan Africa, where HIV is driving the epidemic. However, as noted previously, TB symptoms may be different in people living with HIV and some people may be asymptomatic, which can complicate diagnosis. A prospective cohort study with 1,768 patients living with HIV from eight clinics in Cambodia, Vietnam and Thailand found that TB screening that includes questions about a combination of TB symptoms such as fatigue, fever and weight loss was significantly more effective in ruling out TB than asking about cough alone (Cain et al., 2010).

"Because dual infection with HIV and tuberculosis poses a life-threatening diagnostic and therapeutic dilemma...HIV programs must include capabilities for diagnosis, treatment, and prophylaxis of tuberculosis. Tuberculosis treatment programs should be supported as an important point of entry for HIV testing and consideration for HAART. It is critical to overall treatment success that these coexisting epidemics be addressed in parallel" (IOM, 2005: 6). It is estimated that half a million people with HIV/AIDS could be reached through existing TB programs (Kim, 2004 cited in IOM, 2005: 103). A



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modeling study based on nine-countries in sub-Saharan Africa found that if HIV-positive patients were started on ART within five years of seroconversion, the incidence of AIDS-related TB would be reduced by 48% (Williams et al., 2010b). "If ART was started even earlier, within one year of seroconversion, the direct effect on HIV-related tuberculosis would not be much greater, but such treatment would be expected to reduce HIV transmission substantially, resulting in fewer people infected with HIV and thereby greatly reducing the long-term risk of HIV-associated tuberculosis" (Harries et al., 2010b: 1909).

*Guidelines Aim to Strengthen the Response to HIV/TB Co-Infection*

WHO has released new guidance recommending twelve activities that should be carried out by the health sector response to HIV/AIDS, which focus on the intersection of the TB and HIV epidemics. The twelve activities aim to attain three overarching goals: 1) Establish and strengthen the mechanisms for delivering integrated TB and HIV services; 2) Reduce the burden of TB in people living with HIV and initiate early antiretroviral therapy through: a) isoniazid preventative treatment; b) intensified case finding for active TB; and c) TB infection control; and 3) Reduce the burden of HIV in patients with presumptive and diagnosed TB. The main elements of the new policy focus on routine HIV testing for TB patients, provision of co-trimoxazole for all HIV-TB co-infected patients, and starting all TB patients with HIV on ART as soon as possible (WHO, 2012c: whqlibdoc.who.int/publications/2012/9789241503006_eng.pdf). For a research agenda, please see Sculier et al., 2011.

Despite overwhelming evidence, many public sector health programs have failed to implement the activities that address reducing the burden of TB and HIV in populations affected by both diseases (Dong et al., 2007; WHO, 2009i). In many countries, the national TB program and the national AIDS control program run as parallel systems without a mechanism to link to one another (Reid et al., 2006; Williams et al., 2008). HIV programs play a vital role in identifying those with TB and interrupting transmission through active TB case finding and implementing infection control measures (Reid et al., 2006). Unfortunately, "delays with the scale-up of antiretroviral treatment have exacerbated the tuberculosis epidemic…and thousands of preventable deaths" (Chopra et al., 2009c: 3).

There is very little sex-disaggregated data on TB/HIV that is not pregnancy-related. As a result, there are a number of research and program gaps related to what works for women who are living with both HIV and TB.

**10A. What Works—*Preventing, Detecting and Treating Critical Co-Infections:* Tuberculosis**

1. Initiating HIV treatment before or during TB therapy can reduce the incidence of TB and



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increase patient survival for those living with HIV, including for patients with XDR TB.

2. Isoniazid preventative therapy can reduce the incidence of active TB and increase survival among people living with HIV.
3. Active case finding increases TB detection, particularly in sub-Saharan Africa where HIV is driving the epidemic.
4. Routine screening and treatment of TB and HIV patients in endemic countries can increase detection of co-infection and increase patient survival.
5. Provider-initiated HIV testing and counseling can be acceptable, feasible and lead to high uptake of HIV testing among TB patients.

*Promising Strategies:*

6. Screening for TB during routine antenatal care in high HIV prevalent settings results in increased TB detection rates in women and is acceptable to most women, though stigma may be a barrier.
7. High ART coverage may reduce the number of new and recurrent TB cases.
8. Infection control of TB within health care settings can reduce the incidence of TB among health care workers, particularly nurses.

## 10A. Evidence

1. **Initiating HIV treatment before or during TB therapy can reduce the incidence of TB and increase patient survival for those living with HIV, including for patients with XDR TB.**

- An open-labeled, randomized, controlled trial of 642 patients with HIV/TB co-infection in **South Africa** from 2005 to 2008 found that starting ART during TB therapy reduced mortality by 56%. Four hundred and twenty-nine patients started ART within eight weeks of starting TB therapy while 213 patients started ART after completing TB therapy, which was, on average, 190 days later than the group starting ART during TB therapy. The group starting ART during TB therapy had a death rate of 5.4 per 100 person-years, which was significantly lower than the death rate of 12.1 per 100 person-years among the group starting ART after TB therapy. Among patients with CD4 counts below 200 cells per cubic mm, the rate of death was 46% lower in the group starting ART during TB therapy. The proportion of patients with a suppressed HIV RNA level was significantly higher in the group starting ART during TB therapy. While 12.4% of patients in the group starting ART during TB therapy developed immune reconstitution inflammatory syndrome (IRIS), which was higher than the group starting ART after TB therapy, none of the deaths in the first group were due to IRIS. Approximately half of the study participants were women, yet sex-disaggregated data was not analyzed (Abdool-Karim et al., 2010c). (Gray II) *(treatment, TB, South Africa)*



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- A study in **Ethiopia** that assessed the effect of HAART on patient mortality and TB incidence rates under routine clinical care conditions in 2003 found that HAART resulted in a 65% decline in mortality and the TB incidence rate was lower in the HAART group. HAART improved survival and decreased TB incidence to a level similar to that achieved in developed countries during the early years of HAART. In August 2003, the hospital started providing HAART to patients. All HIV-positive patients who visited the clinic since January 2003 were followed and treated for opportunistic infections. Patients who were followed from January 2003 to August 2003 were the "pre-HAART cohort" and patients followed from August 2003 to August 2005 were the "HAART cohort." The last day of pre-HAART followed was April 1, 2004. After April 1, 2004 all patients of this hospital who met the Ethiopian HAART treatment guidelines had access to HAART at this hospital. Pre-HAART patients who joined the HAART group contributed person-time to both cohorts at different periods. A cohort of 90 men and 95 women, or a total of 185 patients were followed prior to accessing HAART. A cohort of 102 men and 78 women, for a total cohort of 180 patients were followed in the HAART cohort. At the end of the pre-HAART period, 10 patients (5.4%) were lost to follow-up; 8 (4.3%) were transferred to another health institution; 47 (25.4%) died and 120 (64.9%) were under regular follow-up. The pre-HAAART mortality rate was 58.1 per 100 person-years of observation. TB incidence rate with HAART was reduced by almost 90%. Community agents visited patients on a monthly basis in the patient's home. Community agents received training and had completed secondary school. Community agents reported the patient's status to the hospital following each visit to the patient's home (Jerene et al., 2006). (Gray IIIa) *(TB, treatment, Ethiopia)*

- A retrospective, observational study of 667 co-infected with HIV and TB patients in **Thailand** from 2005-2006 found that patients that did not use ART during TB treatment had five times the risk of dying than those that did use ART. The use of ART during TB treatment was the single most important predictor of survival. The risk of death increased the longer that ART was delayed during TB treatment among 126 patients that started ART after TB diagnosis. Risk was reduced for patients starting ART treatment early while using fluconazole. The use of efavirenz- or nevirapine-containing ART was also found to decrease the risk of death when compared with no ART use (Varma et al. 2009). (Gray IIIb) *(treatment, TB, Thailand)*

- An observational study of 68 patients attending a community-based ART clinic in **South Africa** found that initiating ART among patients with undiagnosed TB was not associated with adverse outcomes. Twenty-three (34%) patients started ART after receiving a smear-negative TB diagnosis and before TB diagnosis and TB treatment. The remaining 45 patients (66%) started TB treatment before starting ART. Of the 23 patients starting ART before starting TB treatment, 26% had sudden onset of TB during the first few weeks of ART treatment but none of them developed immune reconstitution inflammatory syndrome (IRIS). Of the 45 patients starting TB treatment before starting ART treatment, 11% developed immune reconstitution inflammatory syndrome (IRIS). The majority of patients were women (73.5%), yet sex-disaggregated data was not analyzed. Results indicated that starting ART does not need to be delayed until TB diagnosis or TB treatment begins. Inadvertent initiation of ART among patients with unrecognized prevalent TB was not associated with adverse consequences. Therefore, "it is not necessary to wait for cultures to be reported prior to starting ART" (Kerkhoff et al., 2011: 1004). (Gray IIIb) *(treatment, TB, South Africa)*

- A retrospective cohort study of 195 patients with XDR TB in **South Africa** from 2002 to 2008 found that HAART significantly reduced the number of deaths among HIV-positive patients co-infected with XDR TB. Forty-seven percent of study participants were HIV-



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positive, of whom 63% were taking HAART. Of the HIV-positive patients who died, a greater number were not taking HAART (66%) compared to those taking HAART (25%). Patients taking HAART had a lower CD4 cell count (average 267 per $mm^3$) than those not taking HAART (average 440 per $mm^3$). Results indicate that treatment with HAART should be used at an early stage of HIV infection among patients co-infected with XDR TB. Drug resistance did not differ by HIV status. Twenty-one patients died before starting treatment for XDR TB; cause of death was unknown. Approximately half of the study population was women, yet it is unknown how many of those women were living with HIV (Dheda et al., 2010). (Gray IIIb) *(treatment, TB, HAART, South Africa)*

- A retrospective cohort study of 1,003 patients, 411 of which received HAART and 592 of which did not, between January 2000 and December 2004 in **Thailand** found that those who did not receive HAART were 20 times more likely to die compared with those on HAART. Within the HAART group, those who delayed HAART initiation after 6 months had a higher mortality rate than those who initiated within 6 months of TB diagnosis. The average CD4 count was 53 when initiating HAART. Among those on HAART the survival rate after TB diagnosis was 96.1% after one year on HAART, 94.0%, after two years on HAART, and 87.7% after three years on HAART. Among those not on HAART, survival was 44.4% after one year; 19.2% after two years; and 9.3% after three years. Those infected with drug-resistant TB were twice as likely to die as compared with those with drug-susceptible TB (Manosuthi et al., 2006). (Gray IIIa) *(TB, antiretrovirals, Thailand)*

- From February 2003 through January 2004, 2,342 patients were registered for TB treatment in Ubon-ratchathani, **Thailand**. Of these, 225 (10%) were confirmed as HIV-positive prior to their TB diagnosis, and of the remaining 2,117 patients, 680 agreed to be tested for HIV, and 104/680 (15%) were found to be HIV-positive. The 329 (14%) TB patients with confirmed HIV diagnoses were followed prospectively to assess the impact of HAART on TB treatment outcomes. Among the 290 TB patients with known outcomes, 71 were on HAART and 219 were not. Death during TB treatment occurred in 7% (5 of 71) on HAART and 43% (94 of the 219) not on HAART. Antiretroviral therapy was associated with a significant reduction in deaths among those on HAART prior to initiating TB treatment (Akksilp et al., 2007). (Gray IV) *(TB, HIV testing, treatment, Thailand)*

- A multi-center cohort study in **Spain** of 2,238 HIV-seroconverters compared TB incidence in pre-HAART and HAART eras and found that the risk of developing TB was 70% lower in the HAART era than in the pre-HAART era (Muga et al., 2007). (Gray IV) *(TB, treatment, Spain)*

## 2. Isoniazid preventative therapy can reduce the incidence of active TB and increase survival among people living with HIV.

- A number of randomized controlled trials have shown that isoniazid preventive therapy reduces the incidence of active TB disease in people living with HIV (Pape et al., 1993; Hawken et al., 1997; Whalen et al., 1997; Mwinga et al., 1998; Halsey et al., 1998; Gordin et al., 2000 cited in Ayles and Muyoyeta, 2006). (Gray I) *(TB, treatment)*

- A **Cochrane review** of 12 randomized controlled trials from 1993 - 2007 with 8,578 HIV positive patients co-infected with inactive TB, found that any anti-TB drug reduced the risk of developing active TB by 32% when compared with placebo. Patients were randomly assigned



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to TB preventative therapy or placebo, or to alternative TB preventative therapy. Risk was further reduced by 62% among patients with a positive TB skin test. Preventative therapy led to an increase in adverse events, which increased the likelihood of stopping treatment among patients on combination therapies. Approximately 47% of patients were women. Sex disaggregated data was not analyzed (Akolo et al. 2010). (Gray I) *(TB, treatment)*

- A randomized, double-blind, placebo-controlled trial of 1,995 adults living with HIV in **Botswana** from 2004–2009 found that 36 months of isoniazid preventative treatment reduced the incidence of tuberculosis by 43% when compared to six months of isoniazid preventative treatment. The benefit of continuous therapy was even higher for patients with a positive tuberculin skin test with a 74% reduction in TB incidence. Seventy-two percent of participants were women, 69% had CD4 counts of 200 cells/cubic mm or more, and 73% had a negative tuberculin skin test. All participants received at least six months of isoniazid preventative treatment; the control group received a placebo for the remaining 30 months while the intervention group continued to receive isoniazid preventative treatment for a total of 36 months. Incidence of TB was significantly higher in the six-month only group at 1.26% compared to 0.72% in the 36-month treatment group. Among participants with a positive skin test, 6% of the six-month only group developed TB compared to 1.6% of the 36-month treatment group. Those with a positive skin test that received only six months of treatment were three times more likely to develop TB than those on continuous treatment. There was no significant benefit of continuous treatment for participants with a negative tuberculin skin test. Participants with CD4 counts of 200 cells/cubic mm or more benefited more from continuous treatment than those with CD4 counts of 200 cells/cubic mm or less. Starting antiretroviral therapy at the start of the study also had protective effects with the highest TB incidence occurring in participants not on ART; use of ART reduced TB incidence by 50% (Samandari et al., 2011). (Gray II) *(treatment, TB, Botswana)*

- A sub-cohort study, nested within a randomized trial, of 558 patients living with HIV who had a positive tuberculin-skin-test result but did not have active TB in **Tanzania** from 2001 to 2008 found that patients completing six months of isoniazid preventative therapy had higher survival rates than patients not completing therapy. The mortality rate among patients completing therapy was 60% lower than that of patients not completing therapy; 488 patients completed six months of isoniazid preventative therapy compared to 70 that did not. The majority of study patients were female (70%) and most patients had a CD4 count less than or equal to 350 cells/cubic mm (29%). Although there was no difference in the number of new active TB infections between the two groups, there was a significant association between completing six months of isoniazid preventative therapy and increased survival (Kabali et al., 2011). (Gray IIIa) *(TB, treatment, Tanzania)*

- A retrospective analysis evaluated the impact of isoniazid preventative therapy on mortality of 3,258 HIV-positive miners in **South Africa** who initiated isoniazid preventative therapy and found that the mortality rate was significantly lower, with a 53% reduction in mortality among those on isoniazid preventative therapy than among those who did not receive isoniazid preventative therapy (Innes et al., 2010). (Gray IIIa) *(TB, treatment, South Africa)*

- A retrospective medical record review of 11,026 HIV-positive patients who were accessing medical care at 29 public clinics in Rio de Janeiro, **Brazil** from September 2003 until September 2005 found that isoniazid preventive therapy offered in conjunction with expanded access to HAART may improve TB control among people with HIV in high burden settings. The study was conducted to determine the rates of TB in patients who received no HAART or isoniazid preventative therapy; only HAART; only IPT; or both HAART and isoniazid



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preventative therapy. The overall incidence rate of TB incidence was 2.28 cases/100 person-years. Among the patients who received no HAART or isoniazid preventative therapy incidence was 4.01 cases/100 person years. Patients who received HAART alone had incidence of 1.90 cases/100 person years, and those receiving isoniazid preventative therapy along had a rate of 1.27 cases/100 person years. The TB incidence among patients receiving both isoniazid preventative therapy and HAART was 0.8 cases/100 person years, with a 76% reduction in risk for developing TB in this group (Golub et al., 2007). (Gray IIIa) *(TB, co-infection, antiretrovirals, treatment, Brazil)*

- An observational cohort study of 3,270 HIV-positive employees at an HIV workplace program, in a setting with high TB incidence, in **South Africa** from 2004 to 2007 examining the association of isoniazid preventative therapy and mortality of employees starting ART found that mortality rates were lower among employees receiving isoniazid preventative therapy before or with ART than employees not receiving isoniazid preventative therapy, after controlling for confounders. The use of isoniazid preventative therapy had a higher protective effect among employees with CD4 cell counts less than 50 cells/cubic mm when compared to employees with CD4 cell counts above 50 cells/cubic mm. Employees were followed from the start of ART to death, leaving employment, or 12 months from ART start date. All employees were screened annually for TB, regardless of HIV status, and those with TB were treated on short-dose rifampicin-based therapy. Information about past medical history, use of drug therapies, CD4 count, and TB symptoms were recorded for all employees in the HIV workplace program. For employees using ART, death rates were recorded as well. Of the 3,270 employees enrolled in the study, 28% started isoniazid preventative therapy before or during the first three months of starting ART, 96% of those starting within the first week, and 40.9% started cotrimoxazole before or during ART. A small percentage of enrolled employees had TB before starting ART (7.2%). Employees started on isoniazid preventative therapy tended to have higher CD4 cell counts, lower viral load, and higher hemoglobin levels. Approximately 7% were women, however, sex disaggregated data was not analyzed. "Although the results of randomized trials of IPT are awaited, our data support the routine use of IPT in HIV care programmes in line with WHO recommendations" (Charalambous et al., 2010: S12). (Gray IIIb) *(treatment, screening, TB, South Africa)*

### 3. Active case finding increases TB detection, particularly in sub-Saharan Africa where HIV is driving the epidemic.

- A prospective observational cohort study of 240 HIV patients in **South Africa** using an intensive TB pretreatment screening tool found that among patients newly starting ART, 36% had TB and the screening tool resulted in a two-fold decrease in incidence in the first four months of ART. The study compared prevalent TB rates to incident TB rates. Prevalent TB was defined as being diagnosed between the time of study enrollment and ART initiation, typically 28 days. Incident TB was defined as having both TB symptoms and diagnosis occur after starting ART. Of the 87 patients diagnosed with TB, 89% had pulmonary involvement. Also, 87% were prevalent TB and 13% were incident TB, with a baseline prevalence rate of 31.5%. The majority of patients were women (72%), of which 14% were pregnant. The average CD4 cell count at baseline was 125 cells/µl and 54% of patients had WHO stage 3 or 4 disease. Results suggest that many incident cases of TB can be detected as prevalent TB cases when patients start ART if routine screening with a sensitive diagnostic test is used (Lawn et al., 2010). (Gray IIIb) *(screening, TB, South Africa)*



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- Instituting a large component of village outreach work in **Lesotho** resulted in increased numbers of TB patients diagnosed and treated in the context of scale up of HIV treatment. Lesotho has the third highest prevalence of HIV and the fourth highest prevalence of TB worldwide and the majority of TB patients are co-infected with HIV. Instituting an antiretroviral therapy program in a health center in a mountainous region of Lesotho resulted in a 10-fold increased in the detection of TB among patients with and without HIV. The study used a retrospective review of the clinical register during 2006, with data drawn from the cohort of patients who were diagnosed with TB before the implementation of the HIV program, from Jan. 1 to June 30, 2006 and those who were diagnosed with TB after the implementation of the HIV program from July 1-Dec. 31, 2006. With the initiation of ART, all patients were actively screened for both HIV and TB. Prior to the initiation of the ART program, only nine cases of TB were diagnosed, of whom three were women; after the ART program was started, 102 patients were diagnosed with TB, of whom 59 were women. Factors leading to the increase in diagnosing TB included a more comprehensive TB diagnostic algorithm, a greater number of health personnel in the health center, and "a large component of village outreach work" (Furin et al., 2007: 1155). (Gray V) *(TB, screening, Lesotho)*

- From the latter part of 2001 to December 2004, in the Thyolo District in **Malawi**, TB/HIV community volunteers screened for TB symptoms. One in five individuals referred for TB testing was smear-positive. Households where a volunteer found chronic cough had an annual TB incidence rate eight times higher than the general population (Zachariah et al., 2006b). (Gray V) *(TB, screening, Malawi)*

- A total of 18,329 individuals received HIV counseling and testing in six districts in Tamil Nadu, **India** in 2007. Of these 1,065 were identified as TB suspects by HIV test counselors and were referred to TB microscopy centers for diagnosis based on symptoms suggestive of TB history (i.e. cough of 3 or more weeks). Of those referred, 83% (or 888 individuals) followed up on the referrals, and 12% were found to be sputum smear-positive (Ramachandran et al., 2009). (Gray V) *(TB, counseling, testing, screening, India)*

## 4. Routine screening and treatment of TB and HIV patients in endemic countries can increase detection of co-infection and increase patient survival.

- A cluster-randomized trial of 1,455 HIV-positive patients co-infected with TB in Rio de Janeiro, **Brazil,** from 2005–2010, assessed the impact of routine screening and treatment of TB in HIV patients and found that 85% of patients completed isoniazid preventative therapy. Only 20% reported adverse events, which lead to early discontinuation of treatment. Patients receiving HAART were more likely to complete isoniazid preventative therapy than patients not receiving HAART. On average, patients completing isoniazid preventive therapy had a significantly higher CD4 cell count (527 cells/cubic mm) at baseline than those not completing therapy (491 cells/cubic mm). Completion rates were similar among men (85%) and women (84%). The study was conducted in 29 public primary care clinics that offered universal access to ARVs to all HIV-positive patients, which is Brazilian national policy. Clinics were randomly assigned a date to start screening patients for TB and providing isoniazid preventive therapy. Clinic healthcare workers were trained on TB and HIV screening methods, disease prevention measures, reading tuberculin skin tests correctly, and pre- and post-test counseling for infected patients. Six field supervisors were hired to support the clinics and conduct real-time evaluation measures. The supervisors also developed a strategy to help physicians remember the dates when patients should be screened for latent TB infection. Study staff created and distributed educational materials to support the



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implementation of isoniazid preventive therapy. Advocacy activities were conducted at the local level to educate and encourage TB-HIV integration and at the national level to increase the scale-up of isoniazid preventive therapy and TB/HIV collaboration. To collect additional data, medical records of all HIV-positive patients attending the 29 clinics were reviewed. Three years after the start of the study 80% of patients had received a tuberculin skin test with an average time of 44 weeks between a patient's first clinic visit and being tested for TB. For eligible patients, isoniazid preventive therapy was started, on average, 8.9 weeks after diagnosis (Durovni et al., 2010). (Gray II) *(treatment, screening, TB, Brazil)*

- A cross-sectional study evaluating the national scale-up in TB/HIV integration services in 23 of the 161 TB clinics in **Rwanda** from 2005–2009 among 207 patients and 40 staff found that scale-up led to 97% of TB patients knowing their HIV status, an increase in the number of patients accessing HIV treatment and care, and a decrease in the risk of death due to TB/HIV co-infection. The first 10 patients and 1-2 staff at each clinic were interviewed to determine openness to HIV testing, knowledge of TB/HIV, and access to treatment. Of the patients interviewed, 158 (76%) were offered an HIV test at the time of TB diagnosis, 99% of whom accepted and received results. Of the patients who were not offered an HIV test, 80% stated they would take an HIV test if it was offered. The most common reasons for refusing an HIV test was not believing themselves to be at risk for HIV or fear of positive test results. Of staff interviewed, 35% knew that TB was the leading cause of death among people living with HIV and 32% reported offering HIV tests to all TB patients. The most common barriers to offering HIV tests were not enough trained staff or space and patient concern about stigma of test. In addition to interviews, researchers looked at patient records to examine treatment outcomes and testing rates. At baseline 542 patients were receiving TB treatment at the 23 clinics; 39% of patients were women and 44% were HIV-positive. Among the HIV-positive TB patients 2.5% were taking co-trimoxazole and 12.3% had started ART. Following the scale-up of TB/HIV integration services the number of TB patients that had an HIV test increased from 48% to 97%, TB/HIV patients on cotrimoxazole increased from 2.5% to 92%, and the number of TB/HIV co-infected patients on ART increased from 12.5% to 49%. The risk of death among TB patients decreased as well (Pevzner et al., 2011). (Gray IIIb) *(treatment, screening, TB, Rwanda)*

- Integration in **six Sub-Saharan African countries** of a five symptom questionnaire asking about cough, fever, weight loss, night sweats in routine HIV care resulted in 64% of 32,731 people screened, with 22% screening positive for TB of whom an average of 12% received a diagnosis of TB and initiated treatment (Howard and El-Sadr, 2010). (Gray IIIb) *(treatment, screening, TB, sub-Saharan Africa)*

## 5. Provider-initiated HIV testing and counseling can be acceptable, feasible and lead to high uptake of HIV testing among TB patients.

- A cross sectional study in 2007 in two districts in **India** with 568 TB patients, 80% reported being referred for HIV testing after presenting for TB treatment. Of the 568 TB patients, 33% were women. Of the 568 TB patients, 13% reported that they had been tested for HIV prior to receiving a diagnosis of TB. Of the 495 TB patients referred for VCT, 97% reported they had HIV testing and counseling and collected their HIV test results (Thomas et al., 2009). (Gray IIIb) *(testing, counseling, TB, India)*

- A case-study examining the feasibility of integrating TB and HIV care for all patients attending the Gisenyi District Hospital in **Rwanda** found that provider-initiated HIV testing



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and counseling (PITC) of TB patients increased the detection of TB and increased the number of TB patients with known HIV status. The introduction of a TB screening survey increased the detection of TB in hospitalized patients and those in outpatient settings. The number of TB patients with known HIV status increased from 82% in 2004, before the start of the program, to 97% in 2006, one year after the start of the program. Of newly diagnosed HIV patients, approximately 75% started cotrimoxazole preventive treatment and about 50% started ART. Provider-initiated HIV testing and counseling (PITC) of TB patients used mainly on-site resources, which increased the ease and decreased the cost of starting a new program. Of note, the only additional resource was the hiring of a new TB-HIV focal point person who supervised and promoted collaboration between staff and integration of services. (Gasana et al., 2008). (Gray IIIb) *(testing, counseling, TB, Rwanda)*

- A cross-sectional study in 2009 in **South Africa** with 290 men and 310 women found that having received TB and HIV information from primary health care facilities was the leading predictor of uptake of HIV testing. Unmarried patients who had received TB/HIV information at TB clinics were more than five times as likely to have been tested for HIV as unmarried patients who had not received such information. Even after controlling for confounding factors, having received information on the link between TB and HIV at the primary health care facility emerged as the strongest predictor of self-reported HIV testing. Female TB patients were more likely to have tested for HIV than men. (Kigozi et al., 2010). (Gray IIIb) *(testing, counseling, screening, TB, South Africa)*

- A pilot study of 2,795 TB patients in **China** in 2007 assessing the prevalence of TB-HIV co-infection and the effect of provider-initiated HIV testing and counseling (PITC) found that the acceptance rate for HIV testing was 99.1% and 2.2% of TB patients were co-infected with HIV. Of the sixty TB patients diagnosed with HIV, 55 were newly diagnosed; the remaining five had been diagnosed before the study began. Thirty percent of the TB patients were women, who had similar acceptance rate of HIV testing (98.6%) when compared to men (99.3%). HIV prevalence was significantly higher among men (2.6%) than among women (1.1%) (Wang et al., 2010b). (Gray IIIb) *(testing, counseling, TB, China)*

- A study evaluated the uptake of provider-initiated HIV counseling and testing among TB patients in three care settings in Kinshasa, **Democratic Republic of Congo.** All patients registered for TB care at three TB clinics between August 2004 and June 2005, were either offered HIV counseling and testing at either the TB clinic, the primary health center to which the TB clinic belonged or were referred to a free-standing VCT center. Between 95-98% of TB patients were HIV tested when the counseling and testing was performed at the TB clinic or primary health center. However, only 68.5% of TB patients who were referred to VCT center followed up on the referral. (Van Rie et al., 2008). (Gray IV) *(TB, testing, counseling, Democratic Republic of Congo)*

- A pilot cross-referral initiative instituted between VCT centers and treatment facilities of the Revised National TB Control Programme in four districts of Maharashtra, **India** found significant numbers of active TB cases among VCT patients and HIV co-infection in TB patients. From 2003 to 2004, 336 or 3% of 9,921 VCT patients were diagnosed with TB. Of the 765 TB cases, 181 or 24% were found to be HIV-positive, representing 11% of the newly detected people living with HIV in the four districts. All VCTs were located in the same facility as a microscopy center that diagnosed TB. A two-day training on TB-HIV and cross-referral was held for VCT counselors and TB treatment supervisors. Quarterly regional review meetings with VCT and TB staff were held to monitor progress and solve problems in cross-referral. VCT included those who came for the first time to a VCT center as well as those who



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come for further counseling after learning their HIV status. Patients at VCT centers who had a cough for more than three weeks were referred for the standard sputum exam for TB. Persons with symptoms of TB, such as fever or weight loss, were referred to a medical officer, with referrals made irrespective of HIV status. TB patients who reported multiple sexual partners and/or STIs were referred to VCT. HIV status of individuals referred was not included in registers to maintain confidentiality (Shetty et al., 2008b). Similar VCT and TB service linkages were established across 14 states in India, with a population of 633 million. In 2006, nearly 60,000 VCT patients were referred for a TB evaluation and 51,000 TB patients were referred to VCT for HIV counseling and testing (Central TB Division, TB India, 2007 cited in Shetty et al., 2008b). (Gray V) *(TB, testing, counseling, co-infection, India)*

## *Promising Strategies:*

### 6. Screening for TB during routine antenatal care in high HIV prevalent settings may result in increased TB detection rates in women and is acceptable to most women, although stigma may be a barrier.

- At two PMTCT program clinics in Soweto, **South Africa,** 370 pregnant women living with HIV were screened for TB symptoms by lay counselors during post-test counseling sessions. Eight women were found to have previously undiagnosed, smear-negative TB disease. Active screening for TB symptoms is feasible (Kali et al., 2006). (Gray IV) *(PMTCT, TB, South Africa)*

- Clients accessing antenatal clients, TB patients, and medical providers from five health facilities in Kasungu District, **Malawi** were interviewed to assess the acceptability of TB screening and TB treatment. Most clients found screening acceptable but expressed concern about HIV stigma. All of the service providers agreed that TB screening was important but expressed concern about the increased workload (Sangala et al., 2006). (Gray IV) *(TB, screening, treatment, stigma, Malawi)*

- Pregnant HIV-positive women who have active TB are at higher risk for mortality. "There is a strong evidence base for screening pregnant HIV-infected women for TB as part of antenatal care. Intensified case finding for TB can reduce morbidity and mortality and prevent transmission of TB in families, the community, and health care settings. Delaying the diagnosis of active TB significantly increases the proportion of infected contacts" (DeLuca et al., 2009: 197). "Although there is a wealth of evidence suggesting that screening for active TB during routine antenatal care would be a beneficial intervention, especially in places with efficient PMTCT program, no country programs have implemented this strategy as part of best practices" (DeLuca et al., 2009: 198). (Gray V) *(TB, screening, antenatal care)*

### 7. High ART coverage may reduce the number of new and recurrent TB cases.

- A descriptive study of 10,070 newly registered TB cases and 755 recurrent TB cases among people living with HIV between 2002 and 2009 in Thyolo District, **Malawi** found that 80% ART coverage led to a decrease in new TB cases by 33% from 2005 to 2009 and a decrease in recurrent TB cases by 25% from 2006 to 2009. ART scale-up prevented an estimated 1,164 new TB cases and 78 recurrent TB cases from 2005 to 2009. ART access reached 80% in



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2007 and remained at that rate in the years following. All HIV-positive patients with WHO Clinical Stage 3 or 4, or a CD4 count of less than 250 cells/$mm^3$ were eligible for ART. HIV/AIDS care and ART were provided free of charge, but isoniazid preventative therapy was not used as a TB treatment strategy in this study. Population data analyzing TB case notification and ART coverage was used to determine the annual association between the number of people on ART and the number of case notifications for new and recurrent TB. From 2005 to 2009 there was a significant decrease in new TB notifications from 259 to 173 cases/100,000 people, which was a 33% reduction. From 2006 to 2009 there was a significant decrease in recurrent TB notifications from 20 to 15 cases/100,000 people, which was a 25% reduction. As the number of people on ART increased the number of new and recurrent TB case notifications decreased significantly (Zachariah et al., 2011c). (Gray IIIb) *(treatment, TB, Malawi)*

- A retrospective descriptive study using mortality records in two major cities in **Zimbabwe,** Harare and Bulawayo found that ART scale up averted premature deaths. ART facilities for the public sector opened in 2004. ART coverage by Dec. 2009 was 56% of those meeting the guidelines for Zimbabwe, which was CD4 counts under 200. Death records were analyzed from 1979 to 2998. From 2004 to 2005, provider-initiated testing and counseling for HIV was introduced at health facilities, particularly for patients with suspected or confirmed TB. TB specific mortality increased 18 fold in Bulwayo and 25 fold in Harare. Mortality from TB per 1,000 population peaked in 2002 at 3.5 and declined starting in 2004 with the advent of ART scale up (Dlodlo et al., 2011). (Gray IIIb) *(treatment, TB, Zimbabwe)*

8. **Infection control of TB within health care settings can reduce the incidence of TB among health care workers, particularly nurses.** *[See. Structuring Health Services to Meet Women's Needs]*

## 10A. Gaps in Programming—Tuberculosis

1. Efforts are needed to reduce TB-related stigma for women.
2. Increased efforts are needed to actively plan for screening and treating HIV-TB co-infection.
3. Further research is needed to determine the appropriate timing of initiating ART for TB/HIV co-infected patients.
4. A combination of infection control strategies may significantly reduce the rate of TB transmission, including drug-resistant TB, in high-risk, low-resourced health care settings.

1. **Efforts are needed to reduce TB-related stigma for women.** A study found that in Malawi, TB-related stigma was closely linked with HIV; in Colombia, women faced work-related stigma; and in India and Bangladesh, women were concerned about the impact of TB on marital prospects and social isolation.



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- Gap noted, for example, in **Bangladesh, India, Malawi** and **Colombia** (Somma et al., 2008); **Cameroon** (Njozing et al., 2010).

2. **Increased efforts are needed to actively plan for screening and treating HIV-TB co-infection, particularly in antenatal clinics.** A study found no planning for HIV-TB co-infection across all levels of the health care system. Other studies found separate services and no information for co-infected patients on the risks of co-infection, plus no screening and treatment of co-infection. *[See also Safe Motherhood and Prevention of Vertical Transmission]*

   - Gap noted for **Vietnam** (Conseil et al., 2010); **South Africa** (Kigozi et al., 2010); **Swaziland** (Elden et al., 2011) and **Ethiopia** (Assefa et al., 2011) and generally (Smart, 2012a).

3. **Further research is needed to determine the appropriate timing of initiating ART for TB/HIV co-infected patients.** Studies conflict with regard to timing of TB therapy and ART for those patients with CD4 counts below 200. Studies also conflict with regard to timing for ART for patients with extra-pulmonary TB.

   - Gap noted generally (Török and Farrar 2011; Marais et al., 2010); **Cambodia** (Blanc et al., 2011); **Vietnam** (Török et al., 2011).

4. **A combination of infection control strategies is needed to reduce the rate of TB transmission, especially in high-risk, low-resourced health care settings.** [*See Structuring Health Services to Meet Women's Needs*] "Early initiation of ART will significantly reduce TB incidence among people on ART, but additional interventions such as screening for TB using highly sensitive tools, preventative therapy, nutrition interventions, anemia, and poverty reduction may be needed to further reduce the burden of TB among people on ART" (Van Rie et al., 2011: 354). A study found that nutrition supplementation may increase patient survival and decrease the recurrence of TB among people living with HIV.

   - Gap noted generally (Van Rie et al., 2011); **India** (Sudarsanam et al., 2011).

## 10B. *Preventing, Detecting and Treating Critical Co-Infections:* Malaria

*"Approximately one million pregnancies per year are complicated by co-infection of malaria and HIV in sub-Saharan Africa" (WHO, 2004 cited in Uneke and Ogbonna, 2009).*

Malaria and HIV co-infection is a critical public health problem that may fuel the spread of both diseases in countries where both diseases are endemic. Malaria seems to be more common for people living with HIV and in areas of unstable malaria transmission, people living with HIV face increased risk of death (Kublin et al., 2005; Hoffman et al., 1999; Mermin et al., 2006; French et al., 2001; Francesconi et al., 2001;



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Grimwade et al., 2004; and Ladner et al., 2003 cited in Mermin et al., 2006). Men and women living with HIV with CD4 counts below 300 cells per cubic mm have both a higher risk of experiencing early treatment failure for malaria and a recurrence of malaria symptoms than HIV-positive people with CD4 counts over 300 or HIV-negative people (Van geertruyden et al., 2006). Clinical malaria has also been associated with an increase in HIV viral load and a fall in CD4 cell count, potentially worsening the clinical outlook for people living with HIV. Repeated and transient increases in HIV viral load resulting from co-infection can amplify HIV prevalence, suggesting that malaria may be an important factor in the rapid spread of HIV infection in sub-Saharan Africa (Abu-Raddad et. al., 2006 cited in Sepulveda et al., 2007).

In areas where malaria occurs, malaria prevention should be part of basic HIV care (Whitworth et al., 2005 cited in Mermin et al., 2006). The U.S. President's Malaria Initiative and other donors are working to integrate HIV/malaria co-infection activities, especially for pregnant women (PMI, 2012).

*Malaria and HIV Co-Infection is of Special Concern to Pregnant Women*

Malaria during pregnancy can result in maternal death, anemia, miscarriage and premature birth, as well as other adverse effects for the infant. The first pregnancies are the most critical, as women develop pregnancy-specific immunity against placental parasites over successive pregnancies as a consequence of repeated exposure (Fried et al., 1998 cited in Gamble et al., 2007). However, available evidence suggests that women who are living with HIV have the same low immunity to malaria in subsequent pregnancies as they do in their first pregnancy and are twice as susceptible to clinical malaria, which can increase the risk of adverse outcomes (Van Eijk et al., 2003 cited in Brentlinger et al., 2006; Flateau et al., 2011). Co-infection increases women's risk of developing severe anemia. It can also restrict fetal growth, reduce the transfer of maternal immunities to other infectious diseases from mother to child, and is associated with pre-term delivery and low birth weight.

Pregnant women with both HIV and malaria who do not have access to antiretroviral therapy may have higher viral loads, which both increases their risk for vertical transmission to their babies and for adverse health effects. A longitudinal study of 1,066 HIV-positive pregnant women, conducted in Dar es Salaam, Tanzania exploring the relationship between malaria parasitemia, CD4 count and viral load of women without access to treatment found that women with low levels of parasitemia at baseline had, on average, a 67% increase in viral load compared to those without parasitemia. Baseline parasitemia itself was not a predictor of AIDS-related death, however, women with a baseline CD4 count greater than or equal to 500 cells/cubic mm, who also had parasitemia, were 2.6 times more likely to be classified with an AIDS-related death (Franke et al., 2010).



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There is recent evidence that shows a link between HIV and malaria co-infection in pregnant women and low birth weight newborns. Low birth weight infants have also been shown to have significantly higher risks of mother-to-child transmission of HIV compared with infants of normal birth weight. However, studies evaluating the impact of HIV and malaria co-infection on mother-to-child transmission of HIV have revealed mixed results, with some showing greater risk, and others reporting no change (Ter Kuile et al, 2004; Kublin et al., 2005 cited in Brentlinger et al., 2006; Desai et al., 2007; WHO, 2005; UNICEF, 2003a; WHO, 2008c; UNICEF, 2009).

Significant gaps remain in how to treat women living with HIV who are sick with malaria, especially during pregnancy. "Studies of the synergy or antagonism between antiretrovirals and antimalarials are …essential to ensure effective and safe malaria case management…and HIV treatment for pregnant women" (Ward et al., 2008: 141). Further evidence on malaria and pregnancy is available at: www.mip-consortium.org.

*The Interactions between HIV and Malaria Are Not Well Understood*

"Although the consequences of co-infection with HIV and malaria parasites are not fully understood, available evidence suggests that the infections act synergistically and together result in worse outcomes" (Skinner-Adams et al., 2008: 264). "Despite the wide prevalence of malaria and HIV in many parts of the tropics, knowledge of how these two important diseases interact is still hampered by lack of knowledge in many key areas…drug interactions form only a very small part of the potentially massive number of ways in which HIV and malaria interact to the detriment of human health" (Khoo et al., 2005).

*Countries with Unstable Rates of Malaria Transmission Require Special Attention*

In areas where malaria occurs at regular intervals, those who survive repeated malarial infections acquire partial immunity by the age of five and carry it into their adult lives. Adults in areas with uncomplicated malaria usually experience mild illness. However in areas where malaria transmission is low and unstable, adults may not have acquired immunity. This means that all age groups are susceptible to severe malaria and its sequelae. Countries with high HIV prevalence and unstable malaria transmission include: Botswana, Namibia, South Africa, Swaziland and Zimbabwe (Idemyor, 2007). In a study of an area of South Africa with unstable malaria transmission, HIV-positive adults with malaria were significantly more likely to die (Grimwade et al., 2004 cited in Slutsker and Marston, 2007). "Unfortunately, the link between the current prevention and control programs for HIV is weak… All those involved in control activities for malaria and HIV… should approach the control of these two diseases in a more integrated way" (Van geertruyden and D'Alessandro, 2007: 467). Blood-smear microscopy is the most common approach to diagnosing malaria. However, low-sensitivity and specificity increases the risk of misdiagnosis and failure to receive treatment. Recent research has found that polymerase chain reaction (PCR) has a higher-sensitivity for diagnosing



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malaria among HIV-positive and HIV-negative pregnant women. Additional research is needed to determine the feasibility and acceptability of use in resource poor settings, as PCR is not readily available due to cost.

*Bednets and Indoor Spraying Can Dramatically Reduce Malaria Transmission*
Effective interventions exist which can dramatically reduce the prevalence and incidence of malaria among both women living with HIV and women who are HIV-negative. A critical intervention is insecticide-treated bednets (ITNs). To be effective, ITNs should be distributed to whole communities in order to achieve area-wide reductions in malaria transmission. In sub-Saharan Africa, the number of households owning at least one ITN increased from 3% in 2000 to 50% in 2011 and surveys indicate that a substantial proportion of people with access to an ITN actually use it (WHO, 2011g). Others estimate that ITN use, defined as "having slept under an ITN the night before" is 60-80% (Slutsker 2012). Long-lasting insecticidal nets have been developed in response to low re-treatment rates of conventional ITNs. These are pre-treated nets that require no further re-treatment during their optimal lifespan of one and a half to three years (Slutsker 2012).

The method and timing of providing bednets should be considered. ITNs distributed through outpatient HIV care programs can result in greater use. However, ITNs distributed only to people living with HIV may become stigmatizing. In addition, because approximately 65% of African women do not present for antenatal care until the second or third trimester, distributing ITNs through antenatal care is not sufficient to protect women in the first or early second trimester before they present to ANC, when malaria can still have deleterious effects on the developing fetus programs may not be effective, as malaria parasites may be well established by the time the woman presents for antenatal care (Brentlinger et al., 2006). ITNs are as effective as indoor residual spraying (Yartey, 2006), as long as ITNs are used consistently and appropriately (Robson, 2009).

Indoor residual spraying (IRS) is another vector control option that involves the application of insecticide to the interior walls of dwellings. Mosquito survival is shortened by exposure to the insecticide thus resulting in overall reduction in malaria transmission. The effectiveness of indoor residual spraying depends on coverage in the community and the level of acceptance. The World Health Organization recommends 12 insecticides for the use of indoor residual spraying, including DDT. DDT is one of the most widely used pesticides as it is the most affordable (Robson, 2009). However, resistance is developing to DDT and new pesticides are needed for indoor residual spraying (Feacham, 2009; Robson, 2009).

In addition, a review of 494 peer reviewed studies from 2005 to 2008 on the health impacts of DDT found that "…exposure to DDT and its breakdown product DDE may be associated with adverse health outcomes such as breast cancer, diabetes, decreased semen quality, spontaneous abortion and impaired neurodevelopment in children" (Eskenazi et



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al., 2009). A recent study of DDT and breast cancer found that pre-pubertal and pubertal years are critical periods of exposure to DDT that may result in increased risk for breast cancer, requiring longitudinal studies of many years (Cohn et al., 2007 cited in Eskanazi et al, 2009). Studies found that indoor residual spraying results in high DDT exposure in humans, including pregnant women and fetuses (Eskanazi et al., 2009). However, no data were found on use of indoor residual spraying for HIV-positive women who are at risk for malaria and on the impact of DDT on immunocompromised women. "Additional research is needed to understand the effects of DDT/E on the immune system and associated diseases, especially since DDT is used in areas where there are often high rates of HIV" (Eskanzi et al., 2009: 25). According to WHO, "new information published since 2000 was evaluated by a WHO Expert Consultation held in December 2010. This information included new epidemiological studies, up-to-date reported levels in human milk, and new information on exposures to DDT occurring as a result of IRS. A detailed exposure assessment was undertaken, including potential exposure to both residents in IRS-treated homes as well as to spray operators. The WHO Expert Consultation concluded that in general, levels of exposure reported in studies were below levels of concern for human health. In order to ensure that all exposures are below levels of concern, best application practices must be strictly followed to protect both residents and workers. Based on the most recent information, WHO has no reason to change its current recommendations on the safety of DDT for disease vector control. However, WHO's position on the safety and use of DDT will be revised if new information on the potential hazards of DDT becomes available justifying such a revision" (WHO, 2011h: 3).

*Intermittent Preventive Treatment Is an Important Strategy in Reducing Malaria in Pregnant Women*

A Cochrane review of six trials involving 2,495 pregnant women having their first or second babies found that antimalarial medications given routinely to women in their first or second pregnancy reduced parasite prevalence and placental malaria. The treatment also had positive effects on birth weight and possibly on perinatal death (Garner and Gülmezoglu, 2006). More research is also needed on the potential interactions of intermittent preventive treatment and antiretroviral medications, particularly during pregnancy (Uneke and Ogbonna, 2009).

**10B. What Works—*Preventing, Detecting and Treating Critical Co-Infections:* Malaria**

1. Co-trimoxazole prophylaxis, antiretroviral therapy and ITNs can substantially reduce the incidence of malaria in women living with HIV.
2. Intermittent preventive treatment of malaria with sulfadoxine-pyrimethamine (SP) is effective in preventing malaria and decreasing prevalence of anemia among pregnant women with HIV.

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*Promising Strategies:*

3. PCR has a higher sensitivity to detect malaria co-infection in HIV-positive and HIV-negative pregnant women.

## 10B. Evidence

### 1. Co-trimoxazole prophylaxis, antiretroviral therapy and ITNs can substantially reduce the incidence of malaria in women living with HIV.

- A meta-analysis of studies assessing the impact of use of insecticide treated bednets (ITNs) on pregnant women found that use of ITNs compared to no use reduced placental parasitemia (malaria parasites in the placenta) by 23% and miscarriages and stillbirths by 33%. Three cluster-randomized and two individually randomized trials, four from **Africa** with 6,418 pregnant women and one from **Thailand** with 223 pregnant women, were included in the meta-analysis. Some women in the cluster-randomized trials became pregnant after ITNs were distributed and were therefore protected throughout pregnancy, when the risk of malaria parasitemia is greatest. ITNs used by the whole community results in area-wide reductions in malaria transmission (Gamble et al., 2007). (Gray I) *(bednets, malaria, Africa, Thailand)*

- A randomized nested case-control study of 836 HIV-infected persons on ART in **Uganda** from 2007 to 2008 examining the effects of discontinuing cotrimoxazole therapy for patients with CD4 counts over 200 cells/µl found that patients discontinuing daily cotrimoxazole therapy were at an increased risk for malaria and diarrhea compared to patients taking daily cotrimoxazole therapy. Ugandan national guidelines recommend all patients living with HIV take daily cotrimoxazole regardless of CD4 count. Participants were recruited from the Home Based AIDS Care program in Uganda, which provided HIV care and drug distribution primarily at home. On average, participants had been taking ART for over three years and CD4 cell count was 489 cells/µl. Seventy-five percent of study participants were women, yet sex-disaggregated data was not analyzed. Within four months of beginning the study, 315 cases of fever had been reported, 72% of which were among patients who had stopped taking cotrimoxazole. Patients who stopped taking cotrimoxazole had 32.5 times the risk of having malaria, 2.7 times the risk of having at least one febrile fever episode, and 1.8 times the risk of having diarrhea than patients taking cotrimoxazole. Patients that stopped taking cotrimoxazole were also more likely to have upper or lower respiratory infections. In the four years prior to the study, there had been no more than five cases of malaria reported within the Home Based AIDS Care program. However, in one month there were over 20 episodes of malaria in the group that had stopped taking cotrimoxazole. As a result of the increased risks to patients, the study was stopped four months after beginning so all patients could resume taking daily cotrimoxazole (Campbell et al., 2012). (Gray II) *(treatment, malaria, Uganda)*

- A prospective cohort study in **Uganda** funded by PEPFAR found that co-trimoxazole prophylaxis, antiretroviral therapy and insecticide treated bednets substantially reduced the frequency of malaria in adults with HIV. Of 466 people living with HIV aged 18 and over, 75% were women, of whom 56 died and 11 were lost to follow-up. Of those who died or were lost to follow up, none had received the intervention. Of the 399 remaining who started co-trimoxazole, 138 survived and were clinically eligible for antiretroviral therapy and received



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both co-trimoxazole and antiretroviral therapy. In addition to these 138 who received both co-trimoxazole and antiretroviral therapy, an additional 897 additional people also received both co-trimoxazole and antiretroviral therapy. Of these 1,035 people who received co-trimoxazole and antiretroviral therapy, 45 died and five moved or were lost to follow-up. The remaining 985 people also received insecticide treated bednets, including four people who started co-trimoxazole, antiretroviral therapy and received ITNs simultaneously. CD4 counts were taken when first enrolled and at regular intervals. Antiretroviral therapy was delivered to homes in prepackaged pillboxes and pills were counted at each visit. According to pill counts, 98% took at least 95% of the prescribed antiretroviral therapy. Two insecticide treated bednets were given to all households with instructions for use. Median follow up before co-trimoxazole was 154 days; during co-trimoxazole and antiretroviral therapy 126 days; and during co-trimoxazole, antiretroviral therapy and ITNs, 560 days. 120,750 home visits were done. Compared with no intervention, co-trimoxazole prophylaxis was associated with a 76% lower malaria rate (9.0 versus 50.8 episodes per 100 person-years); antiretroviral therapy and co-trimoxazole with a 92% lower malaria rate; and co-trimoxazole, antiretroviral therapy and ITNs with a 95% lower malaria rate (50.8 episodes per 100 person years to 2.1 episodes per 100 person years among people living with HIV) than during the time with no intervention of co-trimoxazole (Mermin et al., 2006). (Gray IIIa) *(treatment, bednets, malaria, Uganda)*

- Starting in 2006, the government of **Rwanda** scaled up preventive and curative malaria interventions, increasing access to Artemisinin Combination Therapies (ACT) and delivering 1.6 million ITNs in one week with an additional 1.6 million ITNs distributed by April 2009 through ANC and community health workers, reducing deaths from malaria by 60%. Because everyone in the household received an ITN, pregnant women were ensured access to ITNs. Approximately 60% of pregnant women in 2007 slept under ITNs. Nine of ten private pharmacies now carry ACT. Between 2001 and 2005 only a few hundred thousand ITNs were distributed with negligible impact (Karema, 2009). (Gray V) *(malaria, bednets, Rwanda)*

**2. Intermittent preventive treatment of malaria with sulfadoxine-pyrimethamine (SP) is effective in preventing malaria and decreasing prevalence of anemia among pregnant women with HIV**.

- A **Cochrane review** of two randomized controlled trials (Filler et al., 2006 cited below and Hamer et al., 2007) of 722 HIV-positive pregnant women found that the monthly regimen of sulfadoxine-pyrimethamine (SP) was associated with less placental parasitemia and less peripheral parasitemia than a two-dose regimen in the second and third trimesters among women in their first pregnancies (primigravidae) and women in their second pregnancies (secundigravida). Women who were pregnant for at least a third time (multigravidae) who took the monthly dose had significantly higher levels of haemoglobin compared to women taking the two-dose regimen. Also, babies born to primigravidae and secundigravida women taking the monthly dose had higher mean birth weight compared to babies born to women in the two-dose group. Using three or more doses of sulfadoxine-pyrimethamine (SP) was more effective than using the standard two-dose regimen among HIV-positive pregnant women (Mathanga et al. 2011). (Gray I) *(treatment, malaria)*

- A study of 302 pregnant women from **Mozambique** between August 2003 to November 2006, 88 HIV-positive, 177 HIV-negative, and 37 of unknown HIV status, randomized into a placebo-control trial found that two doses of intermittent preventative treatment (IPT) with sulfadoxine-pyrimethamine (SP) did not enhance the risk of malaria associated morbidity in



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mothers. Presence of maternal malaria was determined by collection of maternal placental tissue immediately following birth and a maternal blood sample eight weeks following delivery. At time of delivery or postpartum, 32% of HIV-positive mothers and 15% of HIV-negative mothers were infected with malaria. Results showed a lower level of antibodies among HIV-positive pregnant women receiving treatment compared to those receiving the placebo (Serra-Casas et al., 2010). (Gray II) *(treatment, malaria, Mozambique)*

- A randomized, double-blind, placebo-controlled trial of 1030 pregnant women in **Mozambique** from 2003 to 2005 found that two-dose SP reduced the incidence of maternal malaria during pregnancy and reduced the prevalence of peripheral parasitemia, regardless of HIV status. Women in the intervention group received two-doses of SP, three tablets twice during the second trimester, one month apart. All women in the study were given long-lasting insecticide treated bed nets and offered an HIV test. Eighty-five percent of women had an HIV test and 23.6% were HIV-positive. The risk of fetal anemia decreased by 50% in the SP group compared to the placebo group. Use of SP also decreased maternal malaria by 40%. Among the women with HIV, the SP group had significantly less parasite infected placentas (6%) than the placebo group (24%) (Menéndez et al., 2008). (Gray II) (*treatment, malaria, Mozambique)*

- A study in **Malawi** from 2002 to 2005 compared monthly doses of Sulfadoxine-Pyrimethamine (SP) Intermittent Preventive Treatment (IPTp) from initiation to delivery with a 2-dose treatment of SP, at initiation and 28 weeks, to prevent placental malaria in 195 HIV-positive and in 303 HIV-negative pregnant women. The study found that monthly dosage proved more effective for HIV-positive women with only 7.8% having placental malaria at delivery compared to 21.5% of women who underwent the 2-dose regimen. Reduction in relative risk was similar for HIV-positive and HIV-negative women: for HIV-negative women, 2.3% receiving monthly SP and 6.3% receiving 2-dose SP had placental malaria, though the difference was not significant. Adverse drug reactions were reported in less than 1% of women. During the study combination antiretroviral therapy was not routinely available in Malawi (Filler et al., 2006). (Gray IIIa) *(treatment, malaria, Malawi)*

## *Promising Strategies:*

### 3. PCR has a higher sensitivity than blood-smear microscopy to detect malaria co-infection in HIV-positive and HIV-negative pregnant women.

- A longitudinal cohort study of 182 pregnant women in the **Democratic Republic of Congo (DCR)** from 2005 to 2006 found that real-time polymerase chain reaction (PCR) had a higher sensitivity and specificity for detecting malaria when compared with blood-smear microscopy. Sensitivity for PCR was 61.9%, more than 20% higher than blood-smear microscopy at 42.0%. Specificity for PCR was also higher at 91.4% than blood-smear microscopy at 83.4%. PCR detected 35 positive cases of malaria that blood-smear microscopy categorized as negative. In order to detect these 35 cases with microscopy the samples would need to be retested, costing over $3,000. The PCR strategy saved $1,553 by correctly detecting the 35 cases as positive, a 51% cost savings. Of the 182 women enrolled in the study 2.7% were HIV-positive and 31% had parasitic malaria either during pregnancy or at delivery (Taylor et al., 2010). (Gray IIIa) *(treatment, screening, malaria, Democratic Republic of Congo)*

- A hospital-based study in **Kenya** followed 157 women ages 15-40 with vaginal deliveries and



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found placental malaria in 17.2% of infants and congenital malaria in 0% of infants by microscopy, while PCR detected 33.1% and 10.8%, respectively (Perrault et al., 2009). (Gray IV) *(PCR, malaria, pregnancy, Kenya)*

## 10B. Gaps in Programming—Malaria

1. Further studies are needed to determine whether standard intermittent preventive treatment and antiretroviral therapy regimens are medically and operationally compatible in pregnancy and to determine safe and effective protocols for management of concurrent HIV and malarial infections in pregnant and non-pregnant women living with HIV.
2. Alternate efficacious drugs for intermittent preventive treatment are needed due to resistance to SP.
3. Additional efforts are needed to reduce HIV stigma so that women will present at health care settings with malaria symptoms and be willing to test for HIV before the development of more serious complications.
4. Further research is needed on infant transmission risks of malaria and/or HIV in pregnant women who have malaria-HIV co-infection.
5. Young women, in particular, need access to services and treatment for HIV and malaria during the perinatal period because they are more likely to be pregnant for the first time.

1. **Further studies are needed to determine whether standard intermittent preventive treatment and antiretroviral therapy regimens are medically and operationally compatible in pregnancy and to determine safe and effective protocols for management of concurrent HIV and malarial infections in pregnant and non-pregnant women living with HIV.** A study found that alternative malarial drug regimens should be considered for HIV/malaria co-infected patients receiving nevirapine.

    - Gap noted generally (Ter Kuile, 2009, Uneke and Ogbonna, 2009, Meshnick et al., 2006 cited in Uneke and Ogbonna, 2009, Brentlinger et al., 2007, Ward et al., 2008, Slutsker and Marston, 2007, Brentlinger et al., 2006)

2. **Alternate efficacious drugs for intermittent preventive treatment are needed due to resistance to SP.** In Tanzania, a country with high rates of SP resistance, SP during pregnancy increased the risk of fetal anemia and decreased cord hemoglobin levels. IPTp did not decrease the risk of placental malaria, maternal anemia, or low birth weight. (Harrington et al., 2011).

    - Gap noted generally (Newman et al., 2003 and EANMAT, 2003 cited in Brentlinger et al., 2006, Ter Kuile, 2009; Slutsker, 2009); **Tanzania** (Harrington et al., 2011); **Mozambique** (Menéndez et al. 2008); **Malawi** (Feng et al., 2010).



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3. **Additional efforts are needed to reduce HIV stigma so that women will present at health care settings with malaria symptoms and be willing to test for HIV before the development of more serious complications.**

   - Gap noted, for example, in **Uganda** (Kamya et al., 2006); **Kenya** (Sande et al., 2010).

4. **Further research is needed on infant transmission risks of malaria and/or HIV in pregnant women who have malaria-HIV co-infection.**

   - Gap noted, for example, in **Kenya** (Perrault et al., 2009, van Eijk et al., 2007, Ayisi et al., 2004); **Malawi, Tanzania and Zambia** (Msamanga et al., 2009); **Uganda** (Brahmbhatt et al., 2008a); and generally (Ayisi et al., 2003 cited in Uneke and Ogbonna, 2009, Naniche et al., 2008).

5. **Young women, in particular, need access to services and treatment for HIV and malaria during the perinatal period because they are more likely to be pregnant for the first time.**

   - Gap noted, for example, in **Kenya** (Ter Kuile et al., 2003 cited in Brabin and Brabin, 2005; Brabin and Brabin, 2005).

## 10C. *Preventing, Detecting and Treating Critical Co-Infections:* Hepatitis

Hepatitis is an inflammation of the liver, most often caused by a virus. The most common types of viruses are hepatitis A, hepatitis B, hepatitis C, hepatitis D and hepatitis E. "Hepatitis A and E are typically caused by ingestion of contaminated food or water and are not known to cause chronic liver disease" (WHO, 2010c) A vaccine exists for hepatitis A and a meta-analysis of eight studies from 1994 to 2004 shows that the vaccine can be effective in HIV-positive people (Shire et al., 2006 cited in Vergidis et al., 2009).

Hepatitis B, C, and D usually occur as a result of contact with infected body fluids (e.g. from blood transfusions, unprotected sexual intercourse with an infected person or from contaminated equipment used in invasive medical procedures or injecting drugs). Hepatitis B can also be passed from mother to infant at birth or during early childhood (Chou, 2009). Hepatitis B and C are important co-infections for HIV and D is only found as a co-infection with hepatitis B.

Approximately a million deaths per year are due to hepatitis B and hepatitis C viruses (WHO, 2010c). Hepatitis E should be studied in HIV co-infected people but no studies have been done to date (Kottilil et al., 2005; Kottilil, 2009). Chronic hepatitis B is recognized in about 10% of people living with HIV globally (Soriano et al., 2010). A recent survey of 2,281 people in Cameroon found high rates of hepatitis B co-infection,



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with 10.5% having chronic hepatitis B and 8.5% living with HIV (Brennan et al., 2012). Another survey in Zambia and South Africa also found that HIV/HBV co-infection "is relatively common" (Hamers et al., 2012b).

*HIV Can Reduce the Body's Response to Hepatitis B Vaccination*

Hepatitis B can be prevented through timely vaccination, ideally within 24 hours after birth. WHO recommends that all infants should receive the first dose of hepatitis B vaccine less than 24 hours after birth, followed by two to three doses to complete the series. Since 2007, more than 88% of member states have introduced hepatitis B vaccine. However, hepatitis B birth-dose global coverage was just 27% in 2007 (Wiersma, 2009). Key countries where infants are not vaccinated are India, Nigeria, China, Indonesia, Ethiopia and Pakistan.

HIV-positive infants, children and adults can also be vaccinated for hepatitis B, but HIV-positive individuals are less likely to respond to vaccination against hepatitis B (Kottilil et al., 2005). A study from 2003 to 2005 in Thailand with 1,535 IDUs (90% male), of whom 24 were HIV-positive found that PWID with HIV were more than six times as likely to not respond to the hepatitis B vaccine, with only 14 responding to the three dose vaccine (Sunthornchart et al., 2008). However, a more recent study found that standard hepatitis B vaccinations in HIV-positive adults with CD4 cell counts above 200 and with undetectable viral load was "highly effective" (Chaiklang et al., 2012). Therefore, initiation of ART is recommended prior to vaccination in people with low CD4 cell counts and titering should be done afterward (Swan, 2012).

Importantly, treatment for hepatitis B is less effective in those who are co-infected with HIV (Kottilil, 2009)."…All HIV-infected persons should be immunized against hepatitis B, because the natural history of hepatitis B is accelerated in the setting of HIV, and co-infection poses specific considerations in selection of antiretroviral agents" (Marrazzo and Cates, 2011: S66). A study in the United States found that hepatitis B co-infection with HIV doubled mortality rates compared to those without hepatitis B co-infection but who were HIV-positive (Chun et al., 2012). Vaccination is critical as "…no reliable treatment to cure HBV infection in HIV-infected persons exists" (Peters and Marston, 2012: 167).

*Hepatitis C and HIV Co-Infection Can Limit Treatment Options*

Hepatitis C virus (HCV) infection is a blood-borne disease with global distribution that affects almost 3% of the world's population; more than 20% of acute HCV infections cause acute viral hepatitis symptoms severe enough to cause patients to seek medical care, but the majority are asymptomatic. "Without therapy in the acute phase, approximately 75% of all infections become persistent. …Individuals with chronic HCV infection usually remain asymptomatic and undiagnosed for decades before chronic hepatitis leads to severe complications" (Cox, 2012).



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Infection with hepatitis C virus causes liver inflammation and scarring. HIV co-infection accelerates progression of liver disease associated with hepatitis C. Many medications used in ARV therapy are cleared through the liver. Thus, co-infection with hepatitis C can complicate ARV therapy for people living with HIV. However, pegylated interferon plus weight-based ribarin treatment results in successful eradication of HCV in about 40% of co-infected patients and when treatment is successful, survival in these patients is substantially improved (Altice et al., 2010; Soriano et al., 2010). But treatment is expensive and most people who inject drugs in countries where HIV/Hepatitis C co-infection is more common – Russia, China, Ukraine, Vietnam – do not have access to treatment for co-infection (Altice et al., 2010). Those in central Europe and Asia also lack access to hepatitis C testing and treatment is largely not available either (Thomas et al., 2011b). Co-infection of HIV and hepatitis C is highest among those who acquired HIV through injecting drug use (Thomas et al., 2011b). However, new treatments are on the horizon (Chung et al., 2012).

The mother-to-infant transmission of hepatitis C is approximately 4-7%. Maternal co-infection with HIV increases the rate of hepatitis C transmission 4-5 fold, but the actual time and mode of transmission are not known (Roberts and Yeung, 2002). An elective C-section is only recommended for women with hepatitis C/HIV co-infection (Kottilil, 2010). A recent study of HIV/HCV co-infected pregnant women in Brazil and Argentina with access to HAART and therefore had lower viral loads reported that they were less likely to transmit hepatitis C to their infants (Cabot et al., 2012). But ARVs are not sufficient to prevent complications of hepatitis C (Thomas et al., 2011b).

"HCV transmission is likely to persist in areas with limited access to antiviral drugs, and poor needle injection and blood product hygiene. The proportion of patients who access and complete treatment remains low"(Cox, 2012). An effective vaccine is needed. Much more research is needed regarding women, specifically, and hepatitis and HIV co-infection. Treatment literacy on hepatitis C and hepatitis C/HIV co-infection is needed both for those at high risk and health providers (Hoover, 2009).

Almost no research focusing specifically on HIV and hepatitis co-infection among women in developing countries has been done. See Singhatiraj et al., 2012 for a discussion of general treatment options for HIV co-infections with hepatitis B and C. In the United States, updated guidelines were released in March 2012: http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/26/hepatitis-c--hcv--hiv-coinfection. For more in-depth coverage of hepatitis infections for people living with HIV, please refer to Treatment Action Group's Guide to Hepatitis B for People Living with HIV (Chou, 2009) and Guide to Hepatitis C for People Living with HIV (Collins and Swan, 2009).



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**10C. What Works—*Preventing*, *Detecting and Treating Critical Co-Infections:* Hepatitis**

*More research is needed regarding women and hepatitis and HIV co-infection. See the Overview for a general discussion.*

**10C. Gaps in Programming—Hepatitis**

*More research is needed regarding women and hepatitis and HIV co-infection. See the Overview for a general discussion.*

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