Maternal Health and Infectious Diseases: A Technical Update

Over the last 20 years, great achievements have been made in the reduction of deaths in women during pregnancy, childbirth, and the first six weeks postpartum. Globally, an estimated 289,000 women died during pregnancy and the postpartum period in 2013, a decline of 45% from 1990.[1] Still, in many parts of the world, maternal mortality remains unacceptably high with wide variation in progress towards Millennium Development Goal 5.[2] In 2010, sub-Saharan Africa and South Asia accounted for 62% of all maternal deaths worldwide, highlighting the importance of addressing maternal mortality issues with context-specific approaches.[3] For example, maternal deaths increased in much of sub-Saharan Africa during the 1990s, and by 2013, 13 countries had a proportion of AIDS-attributable maternal deaths of 10% or more. [4,5] As progress continues and programs evolve to address changes in global epidemiology, all maternal and newborn healthcare providers will need to be able to identify and manage the infectious diseases most likely to affect their patients. This technical brief is intended to highlight some basic information and key elements about selected infections and offer updated guidance about best clinical practice.

HIV/AIDS

The human immunodeficiency virus (HIV) is transmitted through unprotected sex with an infected partner, transfusion with contaminated blood, injection with contaminated needles, and from infected mother to child during pregnancy, delivery, or during breastfeeding. Evidence suggests that pregnancy and the postpartum period are times of increased risk for HIV acquisition.[6,7,8]

Without treatment, women living with HIV are more susceptible to malaria, tuberculosis, herpes zoster, oral candidiasis, and cervical cancer. They are also vulnerable to severe illnesses rarely seen in individuals with normal immune systems, such as cryptococcal meningitis, toxoplasmosis encephalitis, and certain cancers including central nervous system lymphomas. With appropriate care, including antiretroviral therapy (ART), people living with HIV live healthy and productive lives in the same way that those living with other chronic conditions do. Appropriate care and treatment also dramatically

Reduce HIV infection risk by:

- Offering preconception care and counseling, and increasing access to family planning services.
- Eliminating mother-to-child transmission (MTCT). MTCT rates can be minimized with effective provision of antiretrovirals for mother and infant, prompt identification of TB and initiation of treatment, and exclusive breastfeeding for 6 months. Maternal ART reduces the risk of breastfeeding transmission; breastfeeding should only stop once a nutritionally adequate and safe diet without breast-milk can be provided.
- Educating clients about the HIV/STI prevention benefits of voluntary medical male circumcision and early infant male circumcision.
- Encouraging condom use. Male and female condoms are at least 85% effective against sexual transmission of HIV. Continue to emphasize use of condoms during pregnancy.
- Screening for and treating STIs. STIs can increase individuals' susceptibility to HIV as well as increase infectiousness of those living with the virus.
- Employing harm reduction strategies for those at high risk, such as people who inject drugs and sex workers.
- Testing partners and initiating ART for HIV+ partners in discordant relationships. ART reduces the risk of HIV transmission to serodiscordant partners by up to 96%.

decreases the likelihood that HIV will be transmitted to uninfected partners and babies.

For women aged 15 to 49 years, HIV/AIDS is the leading cause of death globally.[9] Most HIV positive women are infected via unprotected sex with a male partner. Recent data suggest that pregnant or postpartum women living with HIV have an estimated eight times greater risk of maternal mortality than those who are not infected.[10,11] While maternal deaths have decreased overall in the past decade, countries with high HIV burdens have had slower declines compared to countries less affected by the HIV pandemic. Data further suggest that most deaths in HIV-infected pregnant and postpartum women are due to non-obstetric infections including pneumonia, tuberculosis, and meningitis.[12] Evidence indicates that women living with HIV with incident TB have a 2.2-fold increased risk of death compared to HIV-infected women without TB, and infants born to women with TB have three times greater risk of death compared to infants born to mothers without TB[13]. Similarly, HIV increases the risk of malaria and malaria increases HIV replication. Placental malaria with HIV coinfection has been shown to predispose to higher rates of neonatal mortality, preterm delivery, low birth weight, and, in some settings, increased risk of mother-to-child transmission of HIV, highlighting the critical need for evaluation and delivery of effective prevention strategies.[14] Pregnant women living with HIV have 5-fold increased risk for maternal death and 3-fold higher risk of severe anemia due to malaria compared to HIV-uninfected women.[15,16] HIV also appears to increase the risk of acquiring other infections in pregnancy, childbirth, and postpartum, with HIV-infected women experiencing three times the risk of puerperal sepsis.

SCREENING AND DIAGNOSIS: HIV testing can be accurately performed with rapid test kits using finger-stick blood samples in either facility or community settings. In generalized epidemic settings, "opt-out" testing, in which the standard approach is to counsel women and offer them testing unless they opt to decline such testing, has long been recommended for non-pregnant women with or without symptoms, for pregnant women, or for women during childbirth or postpartum if previously untested. Counseling and offering testing to women during antenatal care (ANC) provides an opportunity not only to prevent vertical transmission of HIV, but also to link women with ongoing care and treatment for their own health. It is important to note that standard testing may not detect infection during the "window period' (up to 3 to 12 weeks after infection) when the body is producing antibodies to HIV. Therefore, women should also be educated about the signs and symptoms of acute HIV infection: fever, lymphadenopathy, pharyngitis, skin rash, myalgias and arthralgias; and should be retested every three months during pregnancy and breastfeeding. Male partners of pregnant women should also be encouraged to test, as pregnancy is a time of heightened HIV acquisition risk. In many settings "invitation letters" to male partners have been an effective strategy for increasing partner testing rates. Guidelines for HIV screening during ANC vary according to country contexts and available resources. All clients have a right to confidential and respectful care irrespective of HIV status.

CARE AND TREATMENT: HIV replication is suppressed by combination antiretroviral therapy (ART) consisting of three or more drugs. The simplest regimen is a fixed dose that can be taken as a single daily tablet. Current World Health Organization (WHO) guidelines state that the following should initiate ART: 1) all people living with HIV whose CD4 count is under 500; 2) all pregnant and breastfeeding women living with HIV (at a minimum during pregnancy and breastfeeding); 3) all HIV-infected people in sexual relationships with HIV-negative partners; 4) all HIV-infected children under five; and 5) anyone living with HIV who also has active tuberculosis or Hepatitis B co-infection with evidence of severe chronic liver disease.[17] Any person initiating ART should receive adequate adherence support to remain engaged in care. This is particularly true for pregnant women, where extra support should be provided in adherence and retention in care as evidenced by a recent meta-analysis of 51 studies (32% in Africa) which reported that a pooled estimate of 76% ART adherence in pregnancy dropped to 53% adherence in the postpartum period.[18] Everyone on ART requires routine follow-up to

monitor for potential drug toxicity or treatment failure, screening and treatment of co-infections, provision of psychosocial support, and other patient-defined needs. Prevention of opportunistic infections with a daily dose of 960 mg co-trimoxizole preventative therapy (CPT) is also recommended for HIV-infected individuals, including pregnant and breastfeeding women with a CD4 count of less than 350 or WHO clinical stage 2, 3 or 4 irrespective of CD4 count.[19] While there is some evidence to suggest that folic acid reduces the effectiveness of CPT, this has not changed global guidance about independent administration of both drugs. Folic acid is especially important in the first trimester, and CPT is essential throughout pregnancy.[20]

CARE DURING LABOR, BIRTH, AND POSTPARTUM FOR WOMEN WITH HIV AND HIV EXPOSED INFANTS: In addition to routine respectful, evidence-based maternal care, women who present with unknown HIV status should be offered rapid HIV testing during labor or immediately postpartum, so that antiretroviral treatment can be given to mother and prophylaxis for the baby if the mother is HIV-infected. Providers caring for HIV-infected women should minimize vaginal examinations, avoid artificial rupture of membranes and use the partograph to prevent prolonged labor and identify obstructed labor as early as possible.[21] Cesarean section should be provided for obstetric indications only and not for the prevention of vertical transmission of HIV. Careful attention should be given to infection prevention throughout labor and delivery.[22] Active Management of the Third stage of Labor (AMTSL) should be employed to minimize postpartum blood loss, and providers should remain vigilant for possible PPH, as well as maintain a low threshold for treatment in case of any indication of excessive blood loss.[23] For women with previously diagnosed HIV infection, the provider should ask whether the woman is on ART and when the last dose was taken. As part of birth preparedness, pregnant women on ART should be reminded to bring their medications with them to the facility.[24] If the woman has forgotten her ARVs at home, the facility should provide additional doses to be taken on schedule during labor.

Without intervention, up to 50% of perinatal HIV transmission may occur during breastfeeding. Maternal ART dramatically reduces breastfeeding transmission and HIV-exposed breastfeeding infants whose mothers are taking ART should receive daily nevirapine for prophylaxis during the first six weeks.[25] In addition, mothers living with HIV should be encouraged and supported to breastfeed exclusively for six months if there are not affordable, feasible, acceptable, safe and sustainable alternatives.[26] It is critical that mothers living with HIV are counseled about postpartum family planning, the importance of recommended postpartum care for the mother-baby dyad, and ongoing HIV care, treatment, and support.

Tuberculosis

An estimated 2 billion people are infected with tuberculosis (TB) globally.[27] Individuals at increased risk of TB infection are those exposed to TB disease in a home with poor ventilation or who live or work in congregate settings such as hospitals or prisons. People at risk for TB infection progressing to TB disease include those who are immune impaired due to substance abuse, poor nutritional status, systemic disease such as diabetes or renal disease, or who are immunosuppressed due to HIV. Pregnant women living with HIV have 10 times the risk of developing active TB as those who do not have HIV.[28] TB usually affects the lungs (pulmonary TB) but can affect other sites also (extrapulmonary TB). Pulmonary TB should

Reduce the risk of TB by:

- Promptly diagnosing and effectively treating TB to limit exposure.
- Encouraging clients to practice cough etiquette (cover mouth and nose when coughing).
- Providing surgical masks for coughing patients and N95 masks, fitted to the face to ensure proper sizing and seal, for healthcare workers caring for coughing patients.
- Ensuring adequate ventilation in health care facilities and settings where patients live and work.
- Employing safe sputum collection practices, and ensuring standard infection prevention practices.
- Offering at least six months of isoniazid preventative therapy to people living with HIV with positive or unknown tuberculin skin test status, including pregnant women, after ruling out active TB.

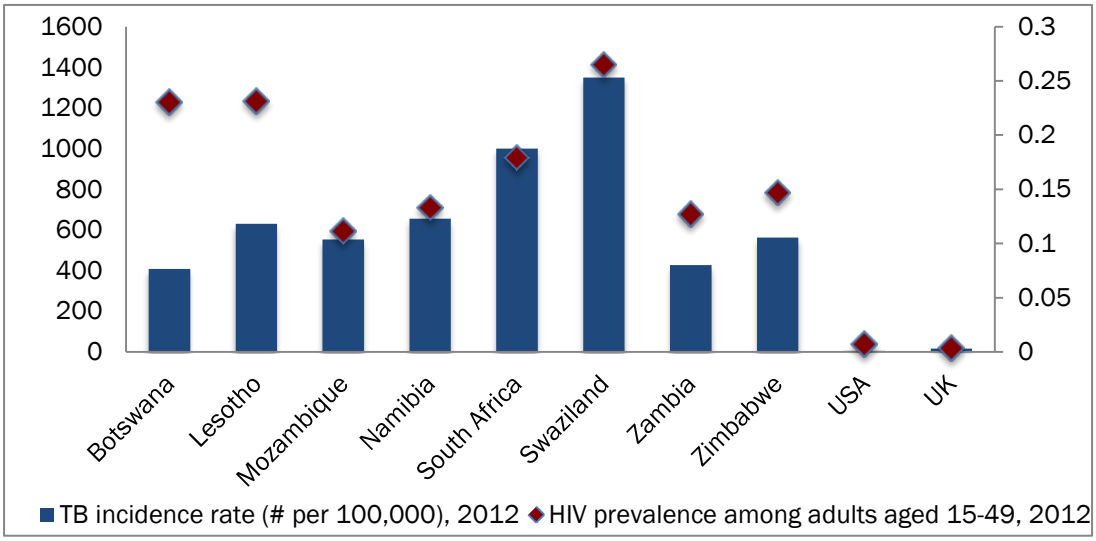
be suspected in individuals presenting with a cough, weight loss or lack of appropriate weight gain in pregnancy, fever, night sweats, or hemoptysis.

TB is responsible for between 6% and 15% of maternal mortality worldwide.[29] While there is no evidence that pregnancy increases the likelihood of new TB infection or reactivation of TB infection,[30] pregnancy can mask TB symptoms (many pregnant women experience fatigue and shortness of breath during pregnancy and weight loss may be difficult to recognize). Pregnant women with pulmonary TB have approximately twice the risk of delivering a baby that is premature or low birth weight and six times the risk of a perinatal death.[31] Congenital infection is rare, although HIV-infected women with active TB are over two times as likely to transmit HIV to infants.[32]

SCREENING AND DIAGNOSIS: Midwives and other clinicians providing routine maternal and newborn care should be aware of the most common signs and symptoms of TB and know the principles of diagnosis, including appropriate referral. Symptom screening for TB (cough, weight loss, night sweats, fever) in ANC is most appropriate in settings with high incidence of TB or high HIV co-infection rates. In such settings, providers should screen for TB symptoms at each encounter using a simple clinical algorithm, and ensure linkages to diagnosis and treatment as appropriate. For example, maternity care providers in Southern African countries should maintain a high index of suspicion for TB among their patients because of the high prevalence of HIV as well as highest incidence of TB globally (see graphic below).

For the past century, sputum smear microscopy has been the most common diagnostic method for pulmonary TB. However, it is not highly sensitive, especially in HIV-infected individuals (due to decreased TB bacillary load). The current gold standard for TB diagnosis is mycobacterial culture, which is not widely available in resource-limited settings. The WHO recommends rapid molecular testing with Xpert MTB/RIF, where available, for people who are HIV positive or who are suspected to have multidrug resistant TB.[33] In addition to increased sensitivity and shorter processing time (less than 2 hours) to detect TB, Xpert MTB/RIF can detect resistance to rifampicin, a proxy indicator for multi-drug resistant (MDR) TB.

Relationship between TB incidence and HIV prevalence rates in selected countries[34,35,36]



CARE AND TREATMENT: WHO recommends the same six-month TB treatment regimen for pregnant and non-pregnant women: ethambutol, isoniazid, rifampicin, and pyrazinamide for two months, then isoniazid and rifampicin for an additional four months.[37] With the exception of streptomycin, which is used in retreatment and is ototoxic to fetuses, first line anti-TB drugs are safe in pregnancy.[38] Anyone diagnosed with TB, including pregnant women, should be

offered HIV testing and counseling. If mothers are being treated with first line drugs, their children should be evaluated for signs and symptoms of TB. If active TB in the baby is ruled out, then s/he should be given six months of isoniazid preventive therapy followed by the BCG vaccination.[39]

CARE DURING LABOR AND BIRTH FOR WOMEN WITH TB: TB transmission can occur anywhere, including the labor ward, if individuals with untreated infectious disease spend time in a closed space. It is therefore essential to ensure that measures to improve respiratory infection control are in place in the facility, in addition to universal precautions such as injection safety. Cross-ventilation and sunlight (exposure to UV) both contribute to decreasing the risk of nosocomial TB transmission. Women with tuberculosis who experience a complication which increases the likelihood of preterm birth can safely be given the standard course of dexamethasone for fetal maturation.

Malaria

Ninety percent of malaria deaths occur in Africa and disproportionately affect pregnant women and young children. Approximately 125 million pregnancies occur each year in areas with *P. falciparum* and/or *P. vivax* malaria transmission; 10,000 of these women and 200,000 of their newborns will die as a result of malaria during pregnancy.[40,41] Malaria in pregnancy (MIP) contributes to maternal anemia, maternal death, stillbirth, spontaneous abortion, and low birth weight.[42,43] In areas of stable malaria transmission,[1] babies are more likely to be small for gestational age, and in areas of unstable malaria transmission, they are more likely to be born preterm. One-third of all neonatal deaths in malaria endemic regions of Africa are due to low birth weight associated with *P. falciparum* infections during pregnancy.[44] The impact of malaria on maternal health depends on age (young mothers are more vulnerable), gravidity (women are at higher risk for the effects of malaria during their first pregnancies), nutritional status, the intensity of malaria transmission, prophylactic treatment, and co-infection with other diseases.[45] HIV infection lessens a pregnant woman's ability to control malaria infections and placental infection with malaria parasites doubles the risk of vertical transmission of HIV.[46]

Reduce the risk of malaria infection by:

- Encouraging the use of **long lasting insecticide treated bed-nets (LLINs)** before, during and after pregnancy.
- Providing **intermittent preventive treatment (IPT)** with sulfadoxine pyrimethamine (SP). (See text box below.)
- Ensuring effective **case management** of malaria in pregnancy when symptoms are present.

WHO recommends the above for pregnant women living in all moderate to high malaria transmission areas in Africa. In areas where malaria transmission is unstable, LLINs and case management should be incorporated into routine programming.

Pregnant women living in areas of high to moderate malaria transmission should receive intermittent preventive treatment with 3 tablets of sulfadoxine 500 mg/ pyrimethamine 25 mg (IPTp-SP) at every ANC visit beginning as early as possible in the second trimester (see text box).[47] IPTp-SP should always be administered as directly observed therapy (DOT).[48] Pregnant women living with HIV and taking CTX, should not receive IPTp-SP[2]. When both drugs are taken, in the best case scenario, this reduces the effect of both drugs and in the worse case scenario can increase adverse reactions. The rate of severe cutaneous reactions was approximately double in people who received both drugs.[49]

IPTp is also not indicated for pregnant women in areas of unstable malaria transmission, which includes southern and northern Africa and much of South East Asia and parts of Latin America.

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[1] Stable malaria transmission areas include endemic areas where transmission occurs all year long or transmission is intense, but with periods of no transmission during the dry season.

[2] Since both CTX and SP are sulpha drugs with redundant mechanisms of action, there is a risk of adverse reactions when they are taken simultaneously.

Pregnant women in all areas of transmission should sleep under a long lasting insecticide treated bed bed-net (LLITN) to prevent malaria. Pregnant women with malaria are at high risk for anemia and should receive the WHO-recommended daily dose of iron (30-60 mg) and folic acid (0.4 mg) during ANC.[3] Folic acid at this dose may be safely used in conjunction with SP. Folic acid at a daily dose equal or above 5mg should not be given together with SP as this counteracts its efficacy as an antimalarial.

SCREENING AND DIAGNOSIS: Routine screening for malaria in pregnancy is not recommended in stable malaria transmission areas since it is expected the pregnant woman will receive IPTp-SP during routine ANC. If a woman has signs or symptoms of malaria (fever, malaise, headache, myalgia, and vomiting) she should be tested. For women with malaria symptoms, parasitemia confirmation should be performed either by microscopy or rapid diagnostic testing. **If a pregnant woman living in a malaria region has fever, headaches or convulsions and malaria cannot be excluded, it is essential to treat the woman for both malaria and eclampsia.**[50]

In October 2012, the WHO Malaria Policy Advisory Committee (MPAC) reviewed guidance based on the most recent evidence of the efficacy and effectiveness of IPTp-SP in light of growing SP resistance. The MPAC determined that frequent dosing of IPTp-SP is effective in reducing the consequences of MIP. The new WHO recommendations state:

In areas of moderate-to-high malaria transmission, IPTp with SP is recommended for all pregnant women at each scheduled ANC visit. WHO recommends a schedule of four ANC visits.

- The first IPTp-SP dose should be administered as early as possible during the 2nd trimester of gestation
- Each additional IPTp-SP dose should be given at least one month apart throughout the remainder of pregnancy
- The last dose of IPTp-SP can safely be administered up to the time of delivery[51]

CARE AND TREATMENT: The WHO recommends artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated *P. falciparum* malaria in the second and third trimesters. ACT is safe in pregnancy, and the choice of ACT should be based on treatment efficacy against local strains of *P. falciparum* malaria. For uncomplicated malaria in pregnancy in the first trimester, oral quinine plus clindamycin (if available) should be given for seven days. Women who are breastfeeding should receive recommended antimalarial treatments, except for primaquine and tetracycline.[52]

CARE DURING LABOR AND BIRTH FOR WOMEN WITH MALARIA: Pregnant women living in areas of stable transmission or those with malaria are more likely to be anemic, so measures should be taken during labor, delivery, and the postpartum period to limit bleeding. Anemic women are unable to tolerate even small to moderate blood loss, so AMTSL, which includes administration of oxytocin or misoprostol to prevent postpartum hemorrhage, as well as rapid identification and treatment of excessive bleeding after birth, are especially important for women with malaria. Pregnant women with severe malaria should also be monitored for pulmonary edema, hypoglycemia, and early onset of labor.[53] They should be managed in a setting able to identify and treat these complications. Babies of pregnant women who have or have had malaria are also at higher risk for low birth weight, and should be monitored closely during labor and after the birth. Women with malaria who experience a complication which increases the likelihood of preterm birth can safely be given the standard course of dexamethasone for fetal maturation. The postpartum period, before women and babies leave facilities as well as during later visits, is also an excellent time to educate women on the importance of using LLINs for themselves and their newborns.

[3] Folic acid above 5mg should not be given to women taking IPTp-SP as it counteracts the antimalarial efficacy of SP.

Sexually Transmitted Infections

Sexually transmitted infections (STIs) are caused by more than 30 different bacteria, viruses, and parasites and are usually spread through sexual contact, although several can also be transmitted vertically from mother to child. STIs are associated with increased rates of preterm premature rupture of membranes, preterm birth, chorioamnionitis, and postpartum as well as newborn infections. Eight pathogens are associated with the greatest burden of STI-related disease, four of which are currently curable: syphilis, gonorrhea, chlamydia, and trichomoniasis. The other four are chronic viral infections for which treatment measures exist: HIV, HBV, herpes simplex virus (HSV), and the human Papilloma virus (HPV). Effective vaccination exists for HBV infection prevention. There are two currently available, highly effective preventive HPV vaccines. One covers HPV types 16 and 18, responsible for 70% of invasive cervical cancers. The second covers 4 HPV types: 16, 18, 6 and 11; the latter two types cause genital warts.

Common symptoms of STIs include vaginal discharge, genital ulcers, and abdominal or pelvic pain,[54] although STIs can also often be asymptomatic, particularly in women. The presence of one STI can also increase the risk of acquiring a second, i.e. genital HSV infection doubles or triples the likelihood of acquiring HIV.[55] STIs are a public health problem in all countries, and cumulatively can cause chronic disease, AIDS, pregnancy complications, infertility, cervical cancer, and death.[56] Neonatal outcomes can also be grave: prematurity; low birth weight; pneumonia; neonatal sepsis; and congenital infection, including severe infant eye infection and eventual blindness, severe neurological impairment and other manifestations. Syphilis warrants particular attention. The WHO estimates that, worldwide, two million pregnant women are infected with syphilis each year and that more than half of them will transmit the infection to their newborns, resulting in approximately 650,000 fetal and neonatal deaths annually.[57]

SCREENING AND DIAGNOSIS: Due to limited laboratory capacity, many low resource settings employ the syndromic management approach to identify STIs. Syndromic management relies on screening for genital symptoms, such as purulent discharge, and using clinical algorithms to guide treatment. It is important to remember that STI symptoms are often nonspecific, and also that women may be asymptomatic. With syphilis, reliable and inexpensive serologic antibody test are widely available, including the rapid plasma reagin (RPR) and the Venereal Disease Research Laboratory (VDRL) test. All women should be screened for syphilis at first antenatal visit.[58] With routine screening and treatment, congenital syphilis is entirely preventable. HIV testing for clients with syphilis is highly recommended as recent evidence suggests that testing positive for syphilis is associated with an approximately 10 times higher risk of HIV acquisition.[59]

Reduce the risk of STI infection by:

- Counseling about safer sex practices including condom use.
- Encouraging voluntary HIV testing for individuals and couples.
- Screening and treating women in ANC.
- Offering vaccination against HPV.
- Always offering partner screening and treatment when STIs are identified.

CARE AND TREATMENT: Effective antimicrobial treatment is available for gonorrhea, chlamydia, trichomonas, and syphilis according to national treatment protocols (note that gonorrhea is becoming increasingly difficult to treat with the emergence of drug-resistance). For countries using the syndromic management approach, diagnosis and treatment will be guided by clinical flowcharts related to genital ulcers, vaginal discharge, and lower abdominal pain (See "Guidelines and Key References" resources). Partners should also be treated. For syphilis, penicillin is the gold standard, and the more remote from delivery, the more effective the treatment in preventing congenital syphilis (treatment should be given at least 30 days before expected delivery). If newborns show signs of syphilis (generalized edema, skin rash, blisters on soles/palms, rhinitis, anal condyloma, enlarged liver/spleen, paralysis of one limb, jaundice,

pallor), they should be transferred to appropriate care. If mothers are seropositive or symptomatic, but babies have no signs, babies should be treated with penicillin whether or not the mother was previously treated (a single dose of IM benzathine penicillin with dosage according to the baby's weight[60]).

CARE DURING LABOR AND BIRTH AND IMMEDIATE POSTPORTUM FOR WOMEN WITH STIs: Women presenting for care in labor with previously unidentified and/or untreated signs or symptoms of STIs should be treated as soon as practically possible according to clinical guidelines. These women may be at risk for developing chorioamnionitis during the labor, intrapartum, and postpartum periods and should be monitored closely. Artificial rupture of membranes should be avoided, and vaginal exams kept to an absolute minimum. Babies should receive prophylactic eye care with topical antibiotics in the first hour after delivery according to national guidelines to prevent chlamydia and gonorrhea infections in the eye of the newborn (*Ophthalmia neonatorum*).[61] For women with a history of herpes simplex virus (HSV) and genital HSV lesions or prodromal HSV symptoms at the time of labor, a Cesarean delivery is recommended as neonatal HSV infection can result in serious morbidity and mortality.[62]

HEPATITIS

Hepatitis is an inflammation of the liver and may be caused by viral infections. The most common virus strains are hepatitis A, B, C, D and E. Hepatitis B and C are of particular public health importance because they cause both acute and chronic disease in millions of people annually and are the most common causes of liver cirrhosis and liver cancer globally.[63,64] In addition, both B and C can be transmitted vertically from mother to fetus.

Hepatitis B (HBV)

More than 350 million people worldwide are infected with HBV, and approximately 1 million people die annually from HBV-related disease.[65] HBV is most often transmitted through vertical transmission from mother to child during pregnancy or at birth, as screening is often lacking in routine ANC. If a mother is infected with HBV, there is a 90% chance of vertical transmission to the infant.[66] HBV can also be transmitted sexually and parenterally (blood-to-blood, often through contaminated needles or transfusion).[67] Acute HBV is the most common cause of jaundice in pregnancy. Other signs and symptoms of HBV infection include concentrated urine, extreme fatigue, vomiting, and abdominal pain. Over 90% of healthy adults who are infected with HBV will mount immune responses that clear the virus within six months. However, among the remaining 10%, HBV can progress to severe chronic liver disease, which includes cirrhosis of the liver and end-stage liver disease.

Reduce the risk of HBV infection by:

- **Offering the HBV vaccine. It is 95% effective in preventing infection.** WHO recommends that all infants receive the vaccine within 24 hours of birth.
- Screening all donated blood for HBV.
- Encouraging condom use.
- Employing harm reduction strategies for those at high risk.
- Using standard infection prevention and waste management practices.

A vaccine is available for HBV that is 95% effective in preventing disease. As of the end of 2011, 180 World Health Assembly Member states include the HBV vaccine as part of their vaccination schedules with worldwide coverage at 93% for all three doses of the vaccine.[68] With the decreasing cost of the vaccine, coverage is only expected to rise.[69] However, HBV still adversely affects millions of people globally. HBV accounts for 1.2% of mortality for women aged 15 to 49 worldwide.[70] In Africa, studies have shown that pregnant women with HIV are three times more likely to have HBV than pregnant women without HIV.[71] Although pregnancy is generally well tolerated by women living with HBV, it is associated with increased rates of antepartum hemorrhage, gestational diabetes, and preterm labor, as well as premature and low birth weight babies.[72] Of the infants that acquire chronic or acute HBV infection at birth, 25% will die in their adult life from severe chronic liver disease or cancer.[73,74]

SCREENING AND DIAGNOSIS: If feasible, all pregnant women should be screened for HBV by testing for the Hepatitis B surface antigen (HBsAg). If universal screening is not possible, priority should be given to those with an increased risk of HBV (people living with HIV, people who are currently or previously were injection drug users, people who have received blood transfusions or organs, and infants born to infected mothers).[75] If the HBsAg is positive, testing is needed to determine acute or chronic infection and the infant should receive the vaccination and the HBV prophylaxis, Hepatitis B immune globulin. If the HBsAg is negative, it can be assumed there is no infection and the mother and infant should be vaccinated, if possible. All patients with HBV should also be offered testing for HIV.[76] For pregnant women diagnosed with HBV, the severity of disease should ideally be assessed with laboratory investigations including liver biochemical tests and coagulations studies, as well as imaging studies (i.e. ultrasonography) if possible.

CARE AND TREATMENT: Irrespective of diagnostic capabilities, supportive care and nutritional support should be given.[77,78] The fundamental goal for treatment of hepatitis B infection is to prevent progression of the disease, particularly to cirrhosis, liver failure, or hepatocellular carcinoma.[79] There are several effective medications to treat chronic active Hepatitis B including pegylated interferon alfa, entecavir, and tenofovir; the first two are not widely available in resource-limited settings, and global initiatives for tenofovir procurement and distribution are specific to this drug as treatment for HIV in combination with other antiretrovirals.

CARE DURING LABOR AND BIRTH FOR WOMEN WITH HEPATITIS B: As is the case with HIV infection, women with HBV infection should not have membranes artificially ruptured, invasive procedures should be limited, and vaginal exams should also be kept to a minimum.[80,81] Chronic HBV should be monitored closely for exacerbation after delivery.[82] Maintaining excellent infection prevention practices is also critical.

Hepatitis C (HCV)

Every year, 3-4 million people are infected with HCV and more than 350,000 people die from HCV related disease. Globally, 150 million people are chronically infected [83] Hepatitis C (HCV) is most often transmitted through exposure to infectious blood. In highly endemic countries, such as Egypt, India, and Mongolia, the main route of transmission is through injections with contaminated syringes. Other common modes of transmission are by contaminated blood infusions, injection drug use, vertical mother to child transmission, and, less commonly, through sexual contact. Vertical transmission during pregnancy or birth is much lower than HBV, at 5-10% chance of transmission.[84] HCV infection can either result in a mild, short-lived illness or a lifelong chronic disease. About 60%-80% of people infected with acute or chronic HCV are asymptomatic.[85] For those who are symptomatic, signs and symptoms for acute infection include abdominal pain, nausea and vomiting, fever and fatigue, sometimes progressing into jaundice.[86] Chronic HCV is mainly asymptomatic until the development of liver disease.[87]

Limited studies have been conducted on the effects of HCV in pregnancy, but one study showed that HCV positive mothers are statistically more likely to have low birth weight newborns, small for gestational age newborns, newborns that require assisted ventilation, and/or a need for neonatal intensive care.[88] Although risk of mother to child transmission of HCV is low, that risk increases by three times when mothers are co-infected with HIV.[89] Unfortunately, there are no vaccines or pre- or post-exposure prophylaxis presently available for HCV, so education, counseling, and early detection and management are especially important.[90]

SCREENING AND DIAGNOSIS: It is necessary to have laboratory confirmation of HCV infection for those with suspected signs and symptoms, or are at an increased risk of infection, such as people who inject drugs, recipients of blood transfusions, or infants with HCV infected mothers.[91] If HCV is suspected, diagnosis is made through the presence of anti-HCV antibodies; if infection is documented (or liver disease suspected for other reason), a biochemical

assessment of liver function should be performed. It is important to note that tests for HCV are unable to distinguish between acute and chronic infection.[92] All patients with HCV should be offered testing for HIV.[93]

CARE AND TREATMENT: Again, HCV cases should be managed in consultation with an expert.[94] Although current HCV medications are contraindicated in pregnancy, high quality antenatal care offers an opportunity to diagnose early HCV infection, and connect women to ongoing care and monitoring.[95] Prevention is essential in controlling HCV infections. WHO recommended prevention strategies include: screening for infections, risk-reduction counseling and services, needle exchange and syringe programs, medical management of infected persons, professional and public education, and surveillance and monitoring of disease trends.[96]

CARE DURING LABOR AND BIRTH FOR WOMEN WITH HEPATITIS C: As is the case with HIV and HBV infections, women with HCV infection should not have membranes artificially ruptured, invasive procedures should be limited, and vaginal exams should also be kept to a minimum.[97,98]

Chrorioamnionitis and Puerperal Infection

Infection of the amniotic fluid or membranes, or chorioamnionitis, can develop during labor when cervical or vaginal microorganisms migrate through the cervical canal during prolonged labor or prolonged rupture of membranes. Risk factors linked to intra-amniotic infection include prolonged labor, prolonged rupture of membranes, multiple vaginal examinations, nulliparity, previous history of chorioamnionitis, meconium-stained amniotic fluid, the presence of genital pathogens such as the organisms linked to STIs, and alcohol and tobacco use.[99,100] Signs of infection are maternal fever (≥38°C), maternal tachycardia (over 100 bpm), fetal tachycardia (over 160 bpm), uterine tenderness, and/or foul smelling amniotic fluid. Chorioamnionitis is also linked to serious adverse outcomes for newborns including asphyxia, early onset neonatal sepsis, pneumonia, meningitis, and perinatal death.[101]

If untreated, chorioamnionitis leads to puerperal sepsis, which accounts for approximately15% of global maternal mortality.[102] Risk of puerperal sepsis increases after invasive procedures, traumatic delivery or obstructed labor, or when placental fragments are retained in the uterus. Signs and symptoms of postpartum bacterial infection include fever (temperature of 38°C or more), chills, lower abdominal pain, uterine tenderness, subinvolution of the uterus, foul-smelling lochia, vaginal bleeding and, eventually, shock. Initially, postpartum infection may be localized to the perineum, vagina, cervix, or uterus, but can spread quickly, especially if women are immunocompromised, to the fallopian tubes, ovaries, pelvic peritoneum, and blood stream (puerperal sepsis).[103]

SCREENING AND DIAGNOSIS: Maternal fever must be present for chorioamnionitis diagnosis. Maternal and fetal tachycardia are also present in at least half of cases.[104] Clinical diagnosis is sufficient, and laboratory confirmation adds little to guide clinical management, since infection is almost always polymicrobial. As well, waiting for confirmation through laboratory analysis can delay treatment, seriously affecting both maternal and newborn health. When maternal fever is identified during labor, chorioamnionitis should be suspected and antibiotic treatment should be initiated. As with chorioamnionits, clinical diagnosis (fever, and foul smelling lochia, chills, or abdominal tenderness) is sufficient to initiate treatment for postpartum infection. Given the serious risk of mortality, and the often rapid spread of infection, prompt action and very close monitoring of clients with suspected or diagnosed postpartum bacterial infection is essential. The most common diagnosis for a postpartum fever is endomyometritis, infection of the endometrium and myometrium.

CARE DURING LABOR, BIRTH, AND POSTPARTUM FOR WOMEN WITH CHORIOAMNIONITIS AND PUERPERAL SEPSIS: If chorioamnionitis is suspected, broad spectrum antibiotics should be given intravenously until

delivery (ampicillin 2 g every six hours plus gentamicin 5 mg/kg body weight every 24 hours). If the woman delivers vaginally, antibiotics can be discontinued postpartum. If the woman delivers by cesarean, antibiotics should be continued and metronidazole should be added (500 mg IV every 8 hours) until the woman is afebrile for 48 hours[105]. It is also necessary to address the underlying factor which led to infection. Based on obstetrical indications (such as favorability of the cervix, degree of clinical severity, and condition of the fetus), induction, augmentation, or cesarean section may be appropriate. If the mother had, within two days of delivery, a temperature over 38 degrees C, an infection treated with antibiotics, membranes ruptured over 18 hours prior to delivery, or the amniotic fluid was foul smelling or purulent, the baby is at risk for a bacterial infection. In these cases, give the baby ampicillin (IM or IV) and gentamicin IM for at least two days, with dosage according to the baby's weight.[106, 107] Keep mother and baby together and encourage breastfeeding.

Antibiotics should also be provided prophylactically when performing certain procedures that increase women's risk of acquiring an infection. In the case of manual removal of the placenta, for example, a single dose of antibiotics (ampicillin 2 g IV OR cefazolin 1 g IV PLUS metronidazole 500 mg IV) should be given 30 minutes prior to the start of the procedure. With cesarean section, antibiotic prophylaxis should be given after the baby's cord is clamped.

If postpartum infection is suspected, prompt therapeutic treatment with broad spectrum antibiotics is essential. Insert an IV line and give fluids rapidly as well as a combination of intravenous ampicillin 2 g every 6 hours, gentamicin 5 mg every eight hours, and metronidazole 500 mg every 8 hours. If there is inadequate clinical response within 48 hours, re-evaluate the woman for alternate sources of infection (i.e. thrombo-embolic disorders, respiratory tract infections, or malaria) or consider an alternate medication regimen. Antibiotics should be continued until women are fever-free for 48 hours.[108] Also, if the mother has a fever or is being treated with antibiotics, the baby is also at risk for bacterial infection. These babies should receive IM ampicillin and gentamycin (dosage per weight) for five days and should be monitored closely.[109]

Reduce the risk of maternal and newborn infections by:

- Using the partograph to monitor the length and progress of labor, and taking action when the action line is crossed.
- Regularly monitoring women's temperatures.
- Limiting vaginal exams to every four hours as needed for clinical decision-making (do not conduct a digital exam if woman's membranes have ruptured and she is not in labor).
- Avoid routine vaginal examinations at shift change.
- Following standard infection prevention practices and "6 cleans" (clean hands, clean perineum, nothing unclean inserted into the vagina, clean birthing surface, clean cord cutting instrument and clean cord ties.
- Giving antibiotics to women with ruptured membranes for ≥18 hours or those with fever and signs of chorioamnionitis.
- Practicing clean cord and eye care, and encouraging immediate and exclusive breastfeeding.
- Giving prophylactic antibiotic treatment with obstetric procedures including manual removal of placenta and cesarean section.

Bringing It All Together

The intersection of maternal health and infectious diseases is an area requiring increased focus and better clinical and programmatic evidence. Several low cost and effective tools already exist to address these challenges. ART for maternal health and to prevent HIV transmission to newborns, routine screening and appropriate treatment for TB and STIs during pregnancy, IPTp-SP for malaria, consistent infection prevention practices, and integration of infectious disease service provision into maternal and child healthcare platforms—to name a few—can accelerate progress towards improving maternal and neonatal health around the globe.

Guidelines and Key References:

HIV/AIDS

- WHO's 2013 document Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1.
- Co-trimoxizole guidelines: http://www.who.int/hiv/pub/guidelines/ctxguidelines.pdf?ua=1 (to be updated in 2014).

TB:

- Current WHO TB treatment guidelines: http://www.who.int/tb/features_archive/new_treatment_guidelines_may2010/en/index.html
- TB/HIV guidelines: http://www.who.int/tb/challenges/hiv/en/

Malaria:

- WHO Policy Brief for Implementation of IPTp with SP- http://www.who.int/malaria/publications/atoz/Policy_brief_IPTp-SP_implementation_11april2013.pdf.pdf
- Guidelines for the Treatment of Malaria, 2nd edition, Geneva, WHO 2010

STIs:

- WHO Training Modules for the Syndromic Management of Sexually Transmitted Infections, 2nd Edition: http://www.who.int/reproductivehealth/publications/rtis/9789241593407index/en/
- WHO Sexually Transmitted Infections (STIs) http://apps.who.int/iris/bitstream/10665/82207/1/WHO_RHR_13.02_eng.pdf
- WHO Guidelines for the Treatment of Sexually Transmitted Infections: http://www.who.int/hiv/topics/vct/sw_toolkit/guidelines_management_sti.pdf

Hepatitis:

- For WHO HBV Guidelines: http://www.who.int/csr/disease/hepatitis/HepatitisB_whocdscsrlyo2002_2.pdf?ua=1.
- For more information on diagnosis and the clinical differences between acute and chronic HBV infection: WHO's Global Alert and Response website for HBV at: http://www.who.int/csr/disease/hepatitis/whocdscsrlyo20022/en/index3.html.110
- For more information on WHO HCV Guidelines: http://www.who.int/csr/disease/hepatitis/Hepc.pdf?ua=1
- For additional information and recommendations from the WHO for HBV and HCV, please visit WHO's Global Alert and Response website at http://www.who.int/csr/resources/publications/hepatitis/en/

Maternal Bacterial Infections in Pregnancy and Puerperium:

- WHO's Integrated Management of Pregnancy and Childbirth Series : http://www.who.int/maternal_child_adolescent/documents/impac/en/
- WHO's Managing puerperal sepsis Education material for teachers of midwifery: midwifery education modules. – 2nd ed.: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/4_9789241546669/en/

Additional Briefs on Maternal Health and Infectious Disease:

- Intersecting Epidemics: An Overview of the Causes of Maternal Death and Infectious Diseases http://www.mchip.net/intersecting-epidemics
- Maternal Mortality and HIV: An Overview http://www.mchip.net/maternal-mortality-hiv

PREVENTION AND MANAGEMENT OF INFECTIOUS DISEASES THROUGHOUT THE CONTINUUM OF CARE

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Acronyms

ACT	Artemisinin-Based Combination Therapy
AIDS	Acquired Immunodeficiency Syndrome
AMTSL	Active Management of the Third Stage of Labor
ANC	Antenatal Care
ART	Antiretroviral Therapy
ARV	Antiretroviral
BCG	Bacillus Calmette-Guérin
CTX	Cotrimoxazole
DNA	Deoxyribonucleic Acid
DOT	Directly Observed Therapy
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSV	Herpes Simplex Virus
IM	Intramuscular
IPT	Intermittent Preventive Treatment
IPTp-SP	Intermittent Preventive Treatment of Malaria During Pregnancy with Sulphadoxine-Pyrimethamine
IV	Intravenous
LLIN	Long Lasting Insecticidal Net
LLITN	Long-Lasting Insecticide-Treated Net
MCHIP	Maternal and Child Health Integrated Program
MDR-TB	Multi-Drug Resistant Tuberculosis
MIP	Malaria in pregnancy
MPAC	Malaria Policy Advisory Committee
MTB	Mycobacterium tuberculosis
MTCT	Mother-to-Child Transmission
PITC	Provider-Initiated Testing and Counseling
PMTCT	Prevention of Mother-to-Child Transmission
PPH	Postpartum Hemorrhage
RIF	Rifampicin
RPR	Rapid Plasma Reagin
SP	Sulphadoxine-Pyrimethamine
STI	Sexually Transmitted Infection
TB	Tuberculosis
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
UV	Ultraviolet
VDRL	Venereal Disease Research Laboratory
WHO	World Health Organization

[1] World Health Organization (WHO), United Nations Children's Fund (UNICEF), United Nations Population Fund (UNFPA), The World Bank, United Nations Population Division. 2014. Trends in maternal mortality: 1990 to 2013. Estimates by WHO, UNICEF, UNFPA, the World Bank and the United Nations Population Division. Geneva: WHO. Retrieved from http://www.who.int/reproductivehealth/publications/monitoring/maternal-mortality-2013/en/.
[2] Millennium Development Goal 5 is to reduce the global maternal mortality ratio between 1990 and 2015 by 75%.
[3] WHO et al. 2014. Trends in Maternal Mortality: 1990-2013.
[4] Kassebaum NJ et al. 2014. Global, regional, and national levels and causes of maternal mortality during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet*. pii: S0140-6736(14)60696-6.
[5] WHO et al. 2014. Trends in Maternal Mortality: 1990-2013.
[6] Gray R et al. 2005. Increased risk of infection of incident HIV during pregnancy in Rakai, Uganda: a prospective study. *The Lancet* 366(9492): 1182-8.
[7] De Schacht, C et al. 2014. High HIV incidence in the postpartum period sustains vertical transmission in settings with generalized epidemics: a cohort study in Southern Mozambique. *J Int AIDS Soc.* 17(1): 18808. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3946505/
[8] Drake A et al. 2014. Incident HIV During Pregnancy and Postpartum and Risk of Mother-to-Child HIV Transmission: A Systematic Review and Meta-analysis. *PLoS medicine 11.2 (2014): e1001608.* Retrieved fromhttp://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001608.
[9] Lozano R et al. 2012. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet.* 380(9859): 2095-2128.
[10] Zaba B et al. 2013. Effect of HIV infection on pregnancy-related mortality in sub-Saharan Africa: secondary analyses of pooled community based data from the network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA). *The Lancet* 381: 1763-1771.
[11] Zaba B et al. 2013.
[12] Calvert C et al. 2013. HIV and the Risk of Direct Obstetric Complications: a systemic review and meta-analysis. *PLoS One* 12(1): 83. doi:10.1371/journal.pone.0074848.
[13] Gupta A et al. 2007. Postpartum tuberculosis incidence mortality among HIV-infected women and their infants in Pune, India, 2002-2005. *Clinical Infectious Diseases 45(2): 241-249*.
[14] Bulterys PL et al. 2014. Editorial Commentary: Preventing Malaria in HIV-Infected Pregnant Women. *Clinical Infectious Diseases* 58(5): 660-662.
[15] Ayisi JG et al. 2013. The effect of dual infection of HIV and malaria on pregnancy outcome in western Kenya. *AIDS* 17:585-594.
[16] Ticconi C et al. 2013. Effect of maternal HIV and malaria infection on pregnancy and perinatal outcome in Zimbabwe. *Journal of Acquired Immune Deficiency Syndromes* 34(3): 289-294.
[17] WHO. 2013. WHO issues new HIV recommendations calling for earlier treatment. Retrieved from http://www.who.int/mediacentre/news/releases/2013/new_hiv_recommendations_20130630/en.
[18] Nachega JB et al. 2012. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. *AIDS* 26(16): 2039.
[19] WHO. 2006. Guidelines on Co-Trimoxazole Prophylaxis for HIV-Related Infections Among Children, Adolescents and Adults: Recommendations for a public health approach. WHO Press: Geneva. Retrieved from http://www.who.int/hiv/pub/guidelines/ctxguidelines.pdf?ua=1.
[20] Bulterys, PL et al. 2014.
[21] Boyer PJ et al. 1994. Factors predictive of maternal-fetal transmission of HIV-1. Preliminary analysis of zidovudine given during pregnancy and/or delivery. *JAMA* 271(24): 1925-1930.
[22] Mandelbrot L et al. 1996. Obstetric factors and mother-to-child transmission of human immunodeficiency virus type 1: the French perinatal cohorts. SEROGEST French Pediatric HIV Infection Study Group. *American Journal of Obstetrics and Gynecology* 175(3 Pt 1): 661-667.
[23] Boyer PJ et al. 1994.
[24] WHO. 2010. Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. WHO Press: Geneva. Retrieved from http://whqlibdoc.who.int/publications/2010/9789241599818_eng.pdf?ua=1.
[25] WHO. 2010. Guidelines on HIV and infant feeding. WHO Press: Geneva. Retrieved from http://whqlibdoc.who.int/publications/2010/9789241599535_eng.pdf?ua=1.
[26] WHO. 2010. Guidelines on HIV and infant feeding.
[27] Lönnroth K et al. 2008. Global epidemiology of tuberculosis: prospects for control. *Seminars in Respiratory and Critical Care Medicine*. 29(5):481.
[28] World Health Organization Global Tuberculosis Report. 2013. Retrieved from http://www.who.int/tb/publications/global_report/en.
[29] Getahun et al. 2012. Prevention, Diagnosis, and Treatment of Tuberculosis in Children and Mothers: Evidence for Action for Maternal, Neonatal, and Child Health Services. *Journal of Infectious Diseases* 205: S216-227.
[30] Davidson PT. 1995. Managing tuberculosis during pregnancy. *The Lancet*. 346(8969):199.
[31] Getahun et al. 2012.
[32] Gupta et al. 2011. Maternal Tuberculosis: A Risk Factor for Mother to Child Transmission of Human Immunodeficiency Virus. *Journal of Infectious Diseases* 205:S216-227.
[33] WHO. 2013. Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update. Retrieved from http://apps.who.int/iris/bitstream/10665/112472/1/9789241506335_eng.pdf WHO/HTM/2013.16
[34] WHO. 2013. Global tuberculosis report 2013. WHO Press: Geneva.
[35] UNAIDS. 2013. AIDSinfo. Retrieved from http://www.unaids.org/en/dataanalysis/datatools/aidsinfo/.
[36] WHO. 2013. WHO Regions of the Americas: United States of America statistics summary (2002-present). Retrieved from http://apps.who.int/gho/data/view.country.20800.
[37] Mnyani CN et al. 2010. Tuberculosis in Pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology* 118(2): 226–231.
[38] WHO. 2010. Treatment of Tuberculosis Guidelines. WHO Press: Geneva. Retrieved from http://www.who.int/tb/features_archive/new_treatment_guidelines_may2010/en/index.html.
[39] WHO. 2010. Treatment of Tuberculosis Guidelines.
[40] Dellicour S et al. 2010. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. *PLoS medicine* 7(1):e1000221.
[41] WHO. 2011. Malaria: global fund proposal development (round 11): WHO policy brief. WHO: Geneva. Available from: http://www.who.int/malaria/publications/atoz/malaria_gf_proposal_dev_who_policy_brief_201106.pdf
[42] WHO. 2004. A strategic framework for malaria prevention and control during pregnancy in the African region. Brazzaville (Congo): WHO Regional Office for Africa. Retrieved from http://whqlibdoc.who.int/afro/2004/AFR_MAL_04.01.pdf
[43] Steketee RW et al. 1996. The problem of malaria and malaria control in pregnancy in sub-Saharan Africa. *The American Journal of Tropical Medicine and Hygiene 55*(1 Suppl): 2-7.
[44] Eisele TP et al. 2012. Malaria prevention in pregnancy, birthweight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. *The Lancet Infectious Diseases* 12(12):942-949.
[45] Garenne M. 2011. Estimating Obstetric Mortality from Pregnancy-Related Deaths Recorded in Demographic Censuses and Surveys. *Studies in Family Planning* 42(4):237-246.
[46] Brahmbhatt H. et al. 2003. The effects of placental malaria on mother-to-child HIV transmission in Rakai, Uganda. *AIDS* 17(17): 2539-2541.
[47] Weidekamm E. et al. 1982. Plasma concentrations of pyrimethamine and sulfadioxide and evaluation of pharmacokinetic data by computerized curve fitting. *Bulletin of the World Health Organization*. 60(1): 115-122. Retrieved from http://whqlibdoc.who.int/bulletin/1982/Vol60-No1/bulletin_1982_60(1)_115-122.pdf.
[48] WHO 2013. WHO Policy Brief for the Implementation of Intermittent Preventive Treatment of Malaria in Pregnancy using Sulfadoxine-Pyrimethamine (IPTp-SP). Retrieved from http://www.who.int/malaria/publications/atoz/iptp-sp-updated-policy-brief-24jan2014.pdf?ua=1
[49] Gimnig JE et al. 2006. Severe cutaneous reactions to sulfadoxine-pyrimethamine and trimethoprim-sulfamethoxazole in Blantyre District, Malawi. *The American Journal of Tropical Medicine and Hygiene* 74(5):738-743.
[50] WHO. 2007. Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors. WHO Press: Geneva. Retrieved from http://whqlibdoc.who.int/publications/2007/9241545879_eng.pdf?ua=1.

[51] WHO. 2012. Updated WHO Policy Recommendation: Intermittent Preventive Treatment of malaria in pregnancy using Sulfadoxine-Pyrimethamine (IPTp-SP). Global Malaria Programme. Retrieved from http://www.who.int/malaria/iptp_sp_updated_policy_recommendation_en_102012.pdf.
[52] WHO. 2010. Guidelines for the treatment of Malaria: Second Edition. World Health Organization: Geneva.
[53] WHO. 2007. Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors. WHO Press: Geneva. Retrieved from http://whqlibdoc.who.int/publications/2007/9241545879_eng.pdf.
[54] WHO. 2013. Sexually Transmitted Infections (STIs): Fact sheet N°110. Retrieved from http://www.who.int/mediacentre/factsheets/fs110/en/index.html.
[55] Looker KJ et al. 2008. An estimate of the global prevalence and incidence of herpes simplex virus type 2 infection. *Bulletin of the World Health Organization*. *86*(10): 805-812A. Retrieved from www.who.int/bulletin/volume/86/10/07-046128/en.
[56] WHO. 2013. 10 Facts on Sexually Transmitted Infections. Retrieved from http://www.who.int/features/factfiles/sexually_transmitted_diseases/facts/en/index.html.
[57] WHO. 2010. Advancing MDGs 4, 5 and 6: impact of congenital syphilis elimination. Retrieved from http://www.who.int/reproductivehealth/publications/rtis/rhr_hrp_10_01/en/index.html.
[58] WHO. 2006. Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice. WHO Press: Geneva. Retrieved from http://whqlibdoc.who.int/publications/2006/924159084X_eng.pdf?ua=1.
[59] Kinuthia J. 2014. Proceedings from CROI 2014: *Incidence and Cofactors of Acute HIV During Pregnancy and Postpartum*. Seattle, WA.
[60] WHO. 2006. Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice.
[61] WHO. 2010. Essential Newborn Care Training Course. WHO Press: Geneva. Retrieved from http://www.who.int/maternal_child_adolescent/documents/newborncare_course/en/.
[62] Brown ZA et al. 2003. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA*. 289(2): 203.
[63] WHO. 2013. Media Center: Hepatitis C - Fact sheet N° 164. Retrieved from http://www.who.int/mediacentre/factsheets/fs164/en/index.html.
[64] WHO. 2013. Global Alert and Response: Hepatitis. Retrieved from http://www.who.int/csr/disease/hepatitis/en/.
[65] WHO Regional Office for Europe. 2011. *Management of hepatitis C and HIV coinfection: Clinical protocol for the WHO European region*. WHO: Copenhagen.
[66] Ohto H et al. Transmission of hepatitis C virus from mothers to infants. The Vertical Transmission of Hepatitis C Virus Collaborative Study Group. *New England Journal of Medicine* 330(11): 744-750.
[67] WHO Regional Office for Europe. 2011.
[68] Centers for Disease Control and Prevention (CDC). 2012. Global Routine Vaccination Coverage, 2011. *Morbidity and Mortality Weekly Report* 61(43): 883-885.
[69] WHO. 2009. Hepatitis B vaccines. *Weekly Epidemiological Record* 84 (40): 405-420.
[70] Lozano et al. 2012.
[71] Kourtis AP et al. 2012. HIV-HBV Coinfection – A Global Challenge. *The New England Journal of Medicine* 366(19): 1749-1752.
[72] Gasim GI et al. 2013. Hepatitis B and C virus infections among pregnant women in Arab and African countries. *The Journal of Infection in Developing Countries* 7(8): 566-578
[73] CDC. 2010. Viral Hepatitis Surveillance – United States, 2010. Centers for Disease Control and Prevention. Retrieved from http://www.cdc.gov/hepatitis/statistics/2010surveillance/Commentary.htm.
[74] WHO Regional Office for Europe. 2011.
[75] WHO. 2013. Media Center: Hepatitis C. Fact sheet N°164 Retrieved from http://www.who.int/mediacentre/factsheets/fs164/en/index.html
[76] WHO Regional Office for Europe. 2011.
[77] WHO. 2013. Hepatitis B: Fact sheet N°204. Retrieved from http://www.who.int/mediacentre/factsheets/fs204/en.
[78] Degertekin B. et al. 2009. Indications for Therapy in Hepatitis B. *Hepatology* 49(S5): S129-S137.
[79] Sorrell MF et al. 2009. National Institutes of Health Consensus Development Conference Statement: management of hepatitis B. *Hepatology* 49(S5): S4-S12.
[80] Pan CQ et al. 2013. Antiviral therapy for chronic hepatitis B in pregnancy. *Seminars in Liver Disease* 33(2): 138–146.
[81] Cheng YW et al. 2009. The association between the length of first stage of labor, mode of delivery, and perinatal outcomes in women undergoing induction of labor. *American Journal of Obstetrics and Gynecology* 201(5): 477-e1.
[82] Pan. 2013.
[83] WHO. 2013. Media Center: Hepatitis C. Fact sheet N°164 Retrieved from http://www.who.int/mediacentre/factsheets/fs164/en/index.html
[84] Ohto H et al. 1994. Transmission of hepatitis C virus from mothers to infants. The Vertical Transmission of Hepatitis C Virus Collaborative Study Group. *New England Journal of Medicine* 330(11):744-750
[85] WHO. 2002. Global Alert and Response: Hepatitis C. Retrieved from http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index3.html
[86] WHO. 2013. Media Center Hepatitis C. Fact sheet N°164 Retrieved from http://www.who.int/mediacentre/factsheets/fs164/en/index.html
[87] WHO. 2002. Global Alert and Response: Hepatitis C. Retrieved from http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index3.html
[88] Pergam SA et al. 2008. Pregnancy complications associated with hepatitis C: data from a 2003-2005 Washington state birth cohort. American *Journal of Obstetrics and Gynecology* 199(1):38-.e1
[89] Zanetti AR et al. 1995. Mother-to-infant transmission of hepatitis C virus. Lombardy Study Group on Vertical HCV Transmission. *The Lancet* 345(8945): 289-291.
[90] WHO. 2013. Media Center: Hepatitis C. Fact sheet N°164 Retrieved from http://www.who.int/mediacentre/factsheets/fs164/en/index.html
[91] WHO. 2013. Media Center: Hepatitis C. Fact sheet N°164 Retrieved from http://www.who.int/mediacentre/factsheets/fs164/en/index.html
[92] WHO. 2002. Global Alert and Response: Hepatitis C. Retrieved from http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index3.html
[93] WHO Regional Office for Europe. 2011.
[94] WHO. 2002. Global Alert and Response: Hepatitis C.
[95] Pergam et al. 2008.
[96] WHO. 2002. Global Alert and Response: Hepatitis C. Retrieved from http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index5.html
[97] Pan. 2013.
[98] Cheng YW et al. 2009.
[99] Seaward PG et al. 1997. International Multicentre Term Prelabor Rupture of Membranes Study: evaluation of predictors of clinical chorioamnionitis and postpartum fever in patients with prelabor rupture of membranes at term. *American Journal of Obstetrics and Gynecology 177*(5): 1024-1029.
[100] Cheng YW et al. 2009.
[101] Aziz N et al. 2009. Neonatal outcomes in the setting of preterm premature rupture of membranes complicated by chorioamnionitis. *Journal of Maternal-Fetal and Neonatal Medicine* 22 (9):780-784.
[102] WHO. 2011. Why do so many women still die in pregnancy or childbirth? Retrieved from www.who.int/features/ga/12/en/index.html.
[103] WHO. 2008. Education material for teachers of midwifery: Managing puerperal sepsis. WHO Press: Geneva. Retrieved from http://whqlibdoc.who.int/publications/2008/9789241546669_6_eng.pdf?ua=1.
[104] Tita AT et al. 2010. Diagnosis and management of clinical chorioamnionitis. *Clinics in Perinatology* 37(2):339-354.
[105] WHO. 2007. Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors.
[106] WHO. 2006. Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice.
[107] WHO. 2013. Pocket Book for the Hospital Care of Children. WHO Press: Geneva. Retrieved from http://www.who.int/maternal_child_adolescent/documents/9241546700/en/.
[108] WHO. 2008. Education material for teachers of midwifery: Managing puerperal sepsis.
[109] WHO. 2006. Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice.
[110] WHO. 2013. Global Alert and Response: Hepatitis B.