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Hepatitis B and hepatitis C in Pakistan: prevalence and risk factors

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Summary

Background—Pakistan carries one of the world's highest burdens of chronic hepatitis and mortality due to liver failure and hepatocellular carcinomas. However, national level estimates of the prevalence of and risk factors for hepatitis B and hepatitis C are currently not available.

Methods—We reviewed the medical and public health literature over a 13-year period ([Au?1] 1994–September 2007) to estimate the prevalence of active hepatitis B and chronic hepatitis C in Pakistan, analyzing data separately for the general and high-risk populations and for each of the four provinces. We included 84 publications with 139 studies (42 studies had two or more sub-studies).

Results—Methodological differences in studies made it inappropriate to conduct a formal metaanalysis to determine accurate national prevalence estimates, but we estimated the likely range of prevalence in different population sub-groups. A weighted average of hepatitis B antigen prevalence in pediatric populations was 2.4% (range 1.7–5.5%) and for hepatitis C antibody was 2.1% (range 0.4–5.4%). A weighted average of hepatitis B antigen prevalence among healthy adults (blood donors and non-donors) was 2.4% (range 1.4–11.0%) and for hepatitis C antibody was 3.0% (range 0.3– 31.9% [Au?2]). Rates in the high-risk subgroups were far higher.

Conclusions—Data suggest a moderate to high prevalence of hepatitis B and hepatitis C in different areas of Pakistan. The published literature on the modes of transmission of hepatitis B and hepatitis C in Pakistan implicate contaminated needle use in medical care and drug abuse and unsafe blood and blood product transfusion as the major causal factors.

Keywords

Hepatitis; Hepatitis B virus; Hepatitis C virus; Pakistan; Injection

Conflict of interest: No conflict of interest to declare.

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Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are among the principal causes of severe liver disease, including hepatocellular carcinoma and cirrhosis-related end-stage liver disease. The World Health Organization (WHO) estimates that there are 350 million people with chronic HBV infection and 170 million people with chronic HCV infection worldwide.^{1,2} Hepatitis B is estimated to result in 563 000 deaths and hepatitis C in 366 000 deaths annually. ³ Given its large population (165 million) and intermediate to high rates of infection,^{1,2} Pakistan is among the worst afflicted nations.

Pakistan has one of the world's highest fertility rates, exceeding four children per woman.⁴ Its approximately 800 000 sq km are slightly less than twice the size of the state of California in the USA and Pakistan is larger than either Turkey or Chile.^{4,5} Pakistan is divided into four provinces, Punjab, Sindh, Northwest Frontier Province (NWFP), and Balochistan, as well as federally administered areas including the capital (Islamabad), Federally Administered Tribal Areas (FATAs), and the western third of Jammu and Kashmir.^{6,7} Considering Pakistan's size and large, growing population, there is a surprising dearth of information about hepatitis prevalence, although more is known about its risk factors. We reviewed the medical and public health literature over a 13-year period for details on the prevalence of HBV and HCV in Pakistan, analyzing data separately for general and high-risk populations and for each of the four provinces. We further reviewed the published literature concerning the risk factors, including the major modes of transmission of HBV and HCV in Pakistan.

Methods

We initially identified the studies of interest from 1994 to 2007 (up to September 30, 2007) by search of the PubMed database of the National Library of Medicine, National Institutes of Health (USA), using two search strategies: [hepatitis AND Pakistan] and [(HBV OR HCV OR Blood Borne) AND Pakistan]. We also searched in Pakmedinet.com, a search engine that includes the non-indexed journals of Pakistan, by using the keywords [hepatitis or HBV or HCV]. We identified additional articles through searches of specific authors working in this field and through the cited references of relevant articles.

Abstracts of 903 articles were reviewed by one author (SAA) and 182 articles were identified based on the likelihood that primary data on the prevalence of chronic HBV or HCV in Pakistan were to be found within. Articles commenting on risk factors for transmission of hepatitis in Pakistan were also identified. Out of 182 articles, 23 could not be retrieved for complete review due to the obscure or unclear nature of the reference, though we included eight of these studies based on the relevant information available in the abstracts. We found 57 articles reporting primary data on the prevalence of chronic HBV and 63 articles reporting primary data on the prevalence of chronic HCV in Pakistan.

Detection of hepatitis B surface antigen (HBsAg) was considered the marker of chronic HBV and detection of hepatitis C virus antibody (HCVAb) was considered the marker of chronic HCV. Data from these articles regarding study time period, region (city and province), study population (general or high-risk), lab techniques used for HBsAg or HCVAb detection, total sample size, and percentages and numbers of HBV and HCV positive cases were extracted. Prevalence data from individual studies were further segregated into age groups or regions of the country if described in the study. Studies that included primarily but not exclusively adult data were still grouped with adults. Some studies had methodological features that could be criticized; they were included only if they provided the HBsAg or HCVAb data on a defined population using reliable laboratory methods. Based on the sample size of individual studies, simple Wilson binomial confidence intervals were calculated for each study,⁸ along with a

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naïve weighted average prevalence (weighted by each study's sample size) in the general and high-risk populations. Due to methodological differences between studies and the very large sample sizes of a few studies, no formal statistical testing for differences between studies was carried out.

Results

HBV in general populations

Eight pediatric^{9–16} and 35 adult^{10,13,15,17–48} studies addressed the seroprevalence of chronic HBV infection in the general population of Pakistan using HBsAg in asymptomatic persons. The weighted average of all the studies in general pediatric populations was 2.4% (range 1.7–5.5%; Figure 1). Studies in adults were either conducted in blood bank donors^{17–37} or in a non-blood donor general population.^{10,13,15,38–48} Overall HBsAg seroprevalence was higher in the non-blood donor population (3.8% weighted average, range 1.4–11.0%) than the blood donor population (2.3% weighted average, range 1.4–8.4%; Figure 1). The overall HBsAg seroprevalence in healthy adults based on combined data from blood donors and non-donors was 2.4% (range 1.4–11.0%).

Few studies have been published from Balochistan, ^{15,39,43} NWFP, ^{21,27,30,33,37,43,45} and rural parts of Sindh. ^{18,48} Three small studies in Balochistan ^{15,39,43} showed a higher prevalence of HBsAg (9.3% weighted average, range 3.9–11.0%) compared to other provinces (Figure 1). Wide variations in different areas within each province were again noted but no clear trends in prevalence rates were identified over time.

HCV in general populations

We found eight pediatric⁹,10,14,16,38,49–51 and 35 adult¹⁰,17,18,22–25,27–30,32–38,40–42,44–47,49,50,52–59 studies assessing HCVAb seroprevalence in general populations. The weighted average HCVAb seroprevalence in pediatric studies was 2.1% (range 0.4–5.4%). In the adults, studies of HCV seroprevalence in non-blood donors¹⁰,38,40–42,44–47,49,50,59 showed higher rates (5.4% weighted average, range 2.1–31.9%) than in blood donors¹⁷,18, 22–25,27–30,32–37,52–58 (2.8% weighted average, range 0.5–20.7%; Figure 2). The overall HCV seroprevalence in healthy adults, based on combined data from blood donors and non-donors was 3.0% (range 0.5–31.9% [Au?2]).

Punjab^{10,17,23–25,28,29,34,35,38,40–42,44–47,49,50,53,54,57,58 reports suggested a higher prevalence of HCV (4.3% weighted average, range 0.4-31.9%) compared to Sindh, 18,22,32,45,52,56 Balochistan,55 and NWFP27,30,33,37,45,59 (Figure 2). Ten^{10,38,40–42}, 44,46,47,49,50 of 12 studies^{10,38,40–42,44–47,49,50,59} in non-blood donors were performed in Punjab. Wide variations in different areas within Punjab were noted (range 0.4-31.9%) and no clear trends were identified over time.}

Prevalence of HBV and HCV in high-risk populations

Few studies have addressed the prevalence of HBsAg and HCVAb in the high-risk populations of Pakistan^{60–93} (Figure 3). Only one study in female sex workers⁶⁷ and one study in male sex workers (hijras, some of whom are eunuchs)⁶⁸ were found to address the HBV seroprevalence in this population (Figure 3). No HCV study in sex workers was identified. Studies in the household contacts of HCV infected patients^{60–66} showed a relatively high prevalence of HCV (19.0% weighted average, range 4.3–38.0%; Figure 3). In multi-transfused population of patients with thalassemia or hemophilia, three studies^{71,72,75} showed a moderately high prevalence of HBsAg (7.8% weighted average, range 5.0–8.4%), while seven studies^{69–75} showed a very high prevalence of HCVAb (47.2% weighted average, range 25–60%; Figure 3). Similarly, a high prevalence of HBsAg^{83,84} (14.6% weighted average, range

12.4–16.6%) and HCVAb^{85,86} (38% weighted average, range 23.7–68%) was described in the studies of patients undergoing chronic dialysis. Studies in healthcare workers showed relatively higher rates of HBV^{76–82} (6% weighted average, range 0–10.3%) and HCV^{79,81, 82} (5.5% weighted average, range 4.0–5.9%, Figure 3) than in the general population (Figures 1 and 2). Studies in pregnant women showed similar rates of HBV^{87–89} (2.9% weighted average, range 1.8–12.6%; Figure 3), but higher rates of HCV^{89–93} (5.3% weighted average, range 3.2–16.5%; Figure 3), compared to the general population (Figures 1 and 2).

Risk factors for HBV and HCV infection in Pakistan

Needles in healthcare settings-Injections in healthcare settings have been well described in the literature as a major mode of transmission of HBV and HCV in developing countries.^{94,95} A few well-controlled studies have demonstrated a relationship between therapeutic injections and the high prevalence of HBV and HCV.^{14,38,60,96–99} Khan et al. interviewed 203 adult patients as they left local clinics in a peri-urban community just outside of Karachi (Sindh), the major port city located in southern Pakistan.⁹⁶ Of the patients, 81% received an injection on the day of interview. Of the 135 patients who provided a serum sample, 44% were HCVAb positive and 19% had antibodies against HBV (HBsAg was not measured). If oral and injectable medications were deemed equally effective, 44% of the patients declared that they would still prefer injectables. Unsterile, used needles were being used in 94% of the injections observed by the study team and none of the 18 practitioners knew that HCV could be transmitted by injections. In a case-control study in Hafizabad (Punjab), Luby et al. found that HCV infected patients were significantly more likely to have received five or more injections in the past 10 years compared to non-infected controls (odds ratio 5.4, confidence interval 1.2–28).³⁸ In a study of household members of patients with HCV in Hafizabad (Punjab), Pasha et al. showed that the household members who had more than four injections per vear were 11.9 times more likely to be infected than others (p = 0.02).⁶⁰ Similarly, Usman et al. found that in patients with acute HBV, the attributable risk for therapeutic injections was 53%.⁹⁷ Other studies by Jafri et al., Bari et al., Shazi and Abbas, and others have also shown similar results from diverse regions of Pakistan. 14,98,99

Luby et al. in a follow-up study in Hafizabad showed that it is possible to improve the practice of unsterile and unnecessary injections by relatively simple community-based interventions. 100 After low-cost community-based efforts to increase awareness, there was a reported decrease in the use of injections overall and an increase in the use of new needles for injections. The assumption that this will lead to decreased transmission of HBV and HCV makes logical sense, but has not been demonstrated.

Receipt of blood and blood products—Very high prevalence rates of HBV and HCV in multi-transfused populations are due to blood transfusions, but limited data are available about the practices of blood banks in Pakistan. Luby et al. studied 24 randomly selected blood banks in Karachi in 1995; while 95% had reagents and equipment to test for HBV, only 55% could screen for HIV and 23% for HCV.¹⁰¹ Fifty percent of blood banks regularly utilized paid blood donors and only 25% actively recruited voluntary blood donors. More recent data about the practices are not available. In 2001, Ahmed reported a higher prevalence of HBV in professional blood donors as compared to voluntary blood donors (9% vs. 0.8%, p < 0.001). 102

Injection drug users (IDUs)—According to the year 2000 National Assessment Study of Drug Use in Pakistan supported by the United Nations Office of Drug Control and Crime Prevention (UNODC), there are 500 000 heroin addicts in Pakistan, of whom 75 000 (15%) are regular IDUs and 150 000 (30%) are occasional IDUs.¹⁰³ Data on the disease burden in this large high-risk population are limited. Kuo et al., in a study conducted in 2003, showed

HCV prevalence of 93% and 75% among IDUs of Lahore (Punjab) and Quetta (Balochistan), respectively,¹⁰⁴ while Achakzai et al., in a smaller study in 2004, showed HBV, HCV, and HIV prevalences of 6%, 60%, and 24%, respectively, in the IDUs of Quetta.¹⁰⁵ A year 2005 pilot survey of IDUs in Karachi (Sindh) showed an HIV prevalence of 26%, confirming the long-anticipated expansion of the HIV epidemic in Pakistan.¹⁰⁶ HBV and HCV seroprevalence rates were not studied in this survey. A follow-up national survey in 2005 showed HIV prevalence of 23% and 0.5% and HCV prevalence of 88% and 91% in IDUs of Karachi (Sindh) and Lahore (Punjab), respectively.¹⁰⁷

Occupational risks—Certain professions like healthcare workers, sex workers, and barbers may be at increased risk of getting HBV and HCV. The best studied amongst them in Pakistan are healthcare workers, showing a relatively higher prevalence (weighted average 6% and 5.5% for HBV and HCV, respectively) than in general population (Figures 1 and 2). The lack of universal immunization against HBV has been highlighted, especially in these high-risk populations, but coverage of HBV immunization has improved in the general population since 2003.¹⁰⁸ According to the WHO–UNICEF estimates of 2005, 73% of the target population (infants <1 year) of Pakistan have been vaccinated for HBV.¹⁰⁸ While trends are encouraging, coverage is still significantly lower than in industrialized countries. Its benefits on HBV incidence may not be apparent for many years, though eventually one would expect substantial benefit from the innovation of HBV vaccination among Pakistani infants.

Shaving by barbers—It has been suspected that barbers may be contributing to the spread of HBV and HCV by using contaminated razors for shaving. Janjua and Nizamy, in a cross-sectional study of barbers in Rawalpindi/Islamabad in 1999, showed that only 13% knew that hepatitis could be transmitted by contaminated razors.¹⁰⁹ During the actual observation, razors were reused for 46% of shaves. It is possible that contaminated razors may be contributing in the transmission of HBV and HCV, but their relative importance is not clear.

Household contacts/spousal transmission—While some studies have shown a relatively higher prevalence in the household members of patients with HBV and HCV, other studies in the spouses of index cases have shown rates similar to controls. $^{60-64}$ Pasha et al. showed the prevalence of HCV in household members of HCV patients to be 2.5 times that of the general population, but no routes of transmission within the household were associated. 60 The international literature suggests that the sexual transmission of HCV is very low. 110 , 111 It is likely that the high prevalence reported in household contacts in Pakistan may be due to the fact that they are exposed to the same community risk factors as the index patient, rather than intra-household transmission per se. In contrast, HBV intra-familial transmission is well documented outside of Pakistan, and HBV is far more infectious as compared to HCV or HIV. 112–114

Discussion

We observed highly variable seroprevalence estimates for both HBV and HCV from different studies in similar populations, even within the same province. Unlike highly contagious diseases like measles that have a more predictable seroprevalence, blood-borne illnesses like hepatitis and HIV are transmitted sporadically or in micro-epidemics. These micro-epidemics may account for the wide variations in prevalence seen within a nation, a province, or even a community. Identification of the causes of these micro-epidemics provides an opportunity to limit the transmission of these diseases.^{115–117} However, methodological differences in sampling strategies may also contribute to differences in seroprevalence within similar regions or populations. For example, one study of the general population did a staged cluster random sampling of the entire city's study population, ¹⁴ while another study of putative 'random

samples' in a different city recruited persons with the aid of newspaper advertisements⁵⁰ that may have distorted the risk profile of respondents compared to the former study.

As seen in this review, studies of HBV and HCV prevalence are often conducted in blood donor populations because of convenience and access to a large sample size. However, these studies may not truly represent the general population. Prevalence in blood donors may be an underestimate of the population prevalence if potential donors with a high-risk profile, like history of jaundice, injection drug use, multiple sexual partners, etc. are screened out by questionnaires. Conversely, prevalence in blood donors may be an overestimate of the general population if professional blood donors were included, who are often injection drug users selling blood for money. Nonetheless, it is clear that both HBV and HCV infections are very common in Pakistan such that serious incidence rates of end-stage liver disease, both cirrhosis and hepatocellular carcinoma, will plague this nation for many years to come.

The published literature regarding risk factors for HBV and HCV transmission in Pakistan is informative. WHO estimates that in Southeast Asia, an average person receives four injections per year, most of which are unnecessary and up to 75% are unsafe or reused.¹¹⁸ Unnecessary injections are given commonly in Pakistan out of the prevalent view in the population that injected medicines are more effective than oral medications.^{119,120} Intramuscular injections are frequently used for fever, fatigue, and general ailments, while intravenous drips are used for the treatment of weakness, fever, and 'severe' diseases.^{96,120,121} Some people use IV drips to cool down during the summer (HQ, personal observation). These injections are given by physicians at clinics, by informal, untrained providers, by health workers who do home visits, and by pharmacists both trained and informal.^{122,123} The healthcare providers may even encourage the injection-seeking behavior because patients are more willing to pay an additional physician's fee for injections but will not pay this added fee for oral medications.¹²³ Syringes are reused and sterility of injections is often not maintained due to financial limitations and lack of risk awareness among the healthcare providers and the population in general.¹²² These injections appear to be the single most significant factor in the spread of HBV and HCV in the general population of Pakistan.

There are about 1.5 million units of blood products transfused each year in Pakistan.¹²⁴ Data on the safety of this transfusion process are scanty – perhaps due to the lack of a system of reporting infectious or non-infectious adverse events.¹²⁵ The transfusion network is poorly organized and likely contributes significantly in the transmission of serious infectious diseases. In fact, the leading hepatologist and public health scientist of Pakistan and editor of the country's premier medical journal for 30 years died in 2004 of cerebral malaria that she acquired through a blood transfusion given during bilateral knee replacement surgery. Her case dramatized the need for regulation and control of the transfusion practices in Pakistan. Under the umbrella of National Blood Policy, comprehensive measures are needed in both public and private sectors of all four provinces. These measures should include a situational analysis and a realistic assessment of the blood requirement in the area, followed by recruitment and maintenance of voluntary, non-remunerated blood donors and standardization and regulation of appropriate blood screening procedures.

IDUs are numerous in Pakistani society and though they have a disproportionately high burden of health problems, they have been inadequately studied. Limited data suggest the likelihood that the prevalences of hepatitis and HIV are very high in this community. Urgent efforts need to be made to better study this population and to apply globally effective programs like needle exchange and condom distribution together with appropriate counseling and therapy for their drug addiction. Unless serious infections are controlled in IDUs, they will continue to be the source of HBV, HCV, and now HIV to the general population in Pakistan.

While universal immunization against HBV has still not been achieved, significant advances have been made. HBV vaccine has been included in the EPI (Expanded Program for Immunization) since 2002. All healthcare providers in the public sector are eligible for free HBV vaccination. Full coverage with HBV vaccination in the general population would be ideal, but at least healthcare workers and other high-risk professionals should be immunized universally.

The Herculean task of reeducating healthcare providers, informal sector providers, high-risk persons, and the general population is worthy of investment, particularly now that HIV has risen markedly among IDUs, resulting in a concentrated, rather than a nascent epidemic.¹⁰⁶, ¹⁰⁷ Urgent comprehensive efforts at the structural, healthcare provider, and individual level are needed to control the spread of these blood-borne infections (Table 1).

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FIGURE 1. Summary of studies reporting HBV prevalence in the general population of Pakistan Each study is represented horizontally. From L-R: reference number, first author, city in which study conducted, year in which study published; Dot and bar represent the point prevalence of HBV with calculated 95% confidence interval; lab technique used to detect HBsAg; and sample size of the study. The vertical line represents the calculated weighted average prevalence of HBV based on all the studies in the particular group.

ELISA (#) =Enzyme linked immunosorbent assay (# represents generation of test); RPHA=Reverse particle hemagglutination assay; ICT=Immuno-chromatographic test; LPA=Latex particle agglutination; MEIA (#)=Micro enzyme immunoassay (# represents generation of test); RIBA=Recombinant immunoblot assay; ??=unknown



FIGURE 2. Summary of studies reporting HCV prevalence in the general population of Pakistan Each study is represented horizontally. From L-R: reference number, first author, city in which study conducted, year in which study published; Cross and bar represent the point prevalence of HCV with calculated 95% confidence interval; lab technique used to detect HCVAb; and sample size of the study. The vertical line represents the calculated weighted average prevalence of HCV based on all the studies in the particular group.

ELISA (#) =Enzyme linked immunosorbent assay (# represents generation of test); RPHA=Reverse particle hemagglutination assay; ICT=Immuno-chromatographic test; LPA=Latex particle agglutination; MEIA (#)=Micro enzyme immunoassay (# represents generation of test); RIBA=Recombinant immunoblot assay; ??=unknown



FIGURE 3. Summary of studies reporting HBV and HCV prevalence in the high risk population of Pakistan

Each study is represented horizontally. From L-R: reference number, first author, city in which study conducted, year in which study published; Dot and bar represent the point prevalence of HBV with calculated 95% confidence interval while cross and bar represent point prevalence of HCV with calculated 95% confidence interval; lab technique used to detect HBsAg or HCVAb; and sample size of the study. The vertical line represents the calculated weighted average prevalence of HBV or HCV based on all the studies in the particular group. ELISA (#) =Enzyme linked immunosorbent assay (# represents generation of test); RPHA=Reverse particle hemagglutination assay; ICT=Immuno-chromatographic test; LPA=Latex particle agglutination; MEIA (#)=Micro enzyme immunoassay (# represents generation of test); RIBA=Recombinant immunoblot assay

Risk factor	Structun	ral level interventions	Health provider level interventions	Individual level interventions
Injections in healthcare settings		Media campaign to educate public about risks of unnecessary injections Availability of low-cost, single use syringes Ensure availability of low-cost oral medicines	 Education regarding: Risks of unnecessary injections Risks of reuse of needles Availability of oral medication alternatives to injectables 	Counseling for: Insistence on oral medications whenever possible Insistence on only new syringes and needles for injections
Injection drug use		Creation of positive opportunities for youth Recognition of the problem in the community Needle exchange programs/single use syringes only Limit availability of drugs Drug treatment programs with opiate agonist availability	 Training regarding: Recognition of signs of drug abuse and the need to screen for HBV, HCV, and HIV Counseling, treatment, and rehabilitation of drug addicts Stigma reduction and willingness to care for addicts 	 Education of the addict regarding the risks of infections caused by sharing needles Counseling of the addict's family to support the patient
Receipt of blood and blood products		Enforcement of legislation regarding mandatory screening of blood at all blood banks Media campaign to encourage volunteer blood donations Ban on paid blood donations	 Education regarding: Importance of comprehensive screening of all blood products Dangers associated with paid blood donations Limited indications for transfusion to avoid overuse 	 Family education regarding: Risks of paid blood donations Insistence on well-screened blood only Avoidance of unnecessary use of blood or blood products
Occupational risk to healthcare workers	• •	Availability of safer injection technologies for blood drawing Proper disposal of contaminated waste	Education regarding: Safety precautions Management of high-risk situations 	Education regarding: Safety precautions Hand washing
Prevention of mother to child transmission		Universal prenatal screening policies for HBV and HIV Ready availability of test kits, drugs, vaccines, and immune globulin	Education regarding:Need for universal screeningManagement of HIV with antiretroviral medications and replacement or exclusive breast feeding	 Mass education regarding benefits of HBV and HIV screening Counseling for reduction in social harm

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Risk factor	Structural level interventions	Health provider level interventions	Individual level interventions
		Management of HBV with vaccine and HepB immune globulin in neonates	
Sexual transmission	 100% condom policy in sex industry 'ABC' advocacy and education Expanded STD services 	 Education regarding: Management of STDs 'ABC' 'ABC' Stigma reduction and willingness to care for at-risk population 	 Education of sex workers regarding condom use Counseling of discordant couples in condom use
HBV, hepatitis B virus; HCV, h	epatitis C virus; STD, sexually transmitted disease; ABC,	, 'Abstinence' for youth, 'Be faithful' for sexually active, and	1 'Condom availability and education' specially for

spe ĩ lly a yo <u>7</u> a A high-risk persons and venues.