

Analysis of HIV Genotypes in Michigan, 2004-2014

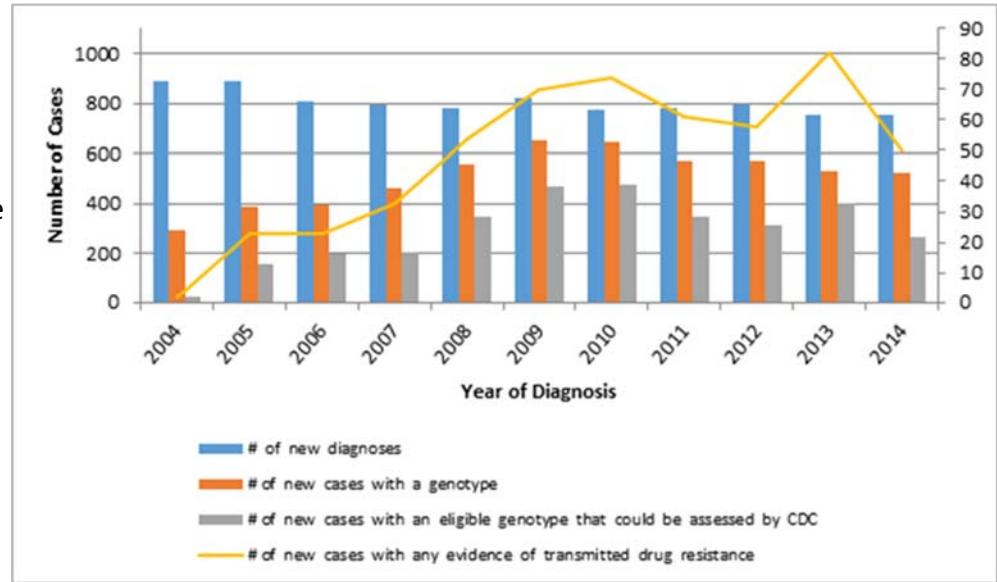


Introduction

The state of Michigan has collected baseline viral genotype sequence data on newly diagnosed HIV positive individuals since October of 2004. Prior to June of 2010 remnant diagnostic HIV serum specimens were collected statewide from sites such as hospitals, private physicians, community-based organizations, blood banks, and local health departments and sequenced free-of-charge to patients as part of a CDC-funded initiative called VARHS (Variant Atypical and Resistant HIV Surveillance). Additionally, private labs began submitting electronic sequences conducted during routine HIV care as early as 2006. In June 2010, CDC funding to genotype under the VARHS protocol ended and since that time genetic surveillance has relied solely on genotypes run in the course of care by practitioners and reported to the Michigan Department of Health and Human Services (MDHHS) (MCL 333.5114). **Figure 1** shows a completeness cascade of collected genotypes from 2004 through 2014. For each year the total number of new HIV cases diagnosed in Michigan and the fraction of those cases with a

viral genotype collected by MDHHS are presented. These are followed by the number of viral genotypes collected by MDHHS that represent baseline sequences – defined as those run on newly diagnosed (<3 months) cases that are unlikely to already have initiated antiretroviral therapy. Finally, the number of new cases with evidence of transmitted drug resistance (TDRM) is presented.

Figure 1: Genotype Completeness in Michigan, 2004-2014

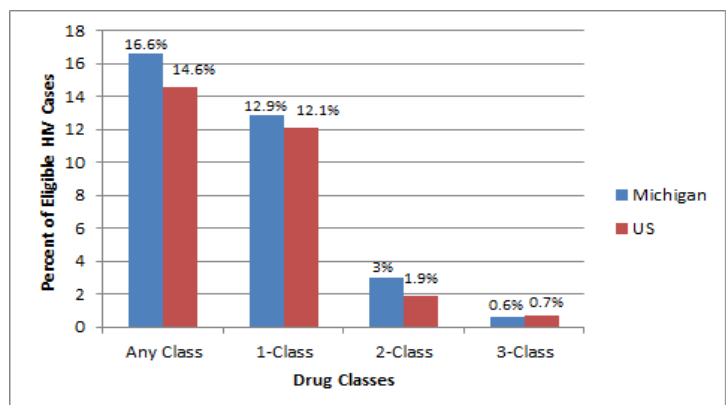


Of note is the decrease in the number of genotypes collected by MDHHS after 2010 attributable to the

Transmitted Drug-Resistant Mutation (TDRM)

In the period from 2004 through 2014, 16.6% (n=530) of new Michigan HIV cases with an eligible genotype collected by MDHHS within 3 months of the patient’s diagnosis date showed evidence of TDRM. Because these newly diagnosed individuals have yet to start treatment, the presence of any HIV drug resistance mutations in their HIV sequence indicates that the resistant virus was

Figure 2: Percent of Eligible Cases with TDRM, by Number of Drug Classes, 2004-2014 (N = 3196)



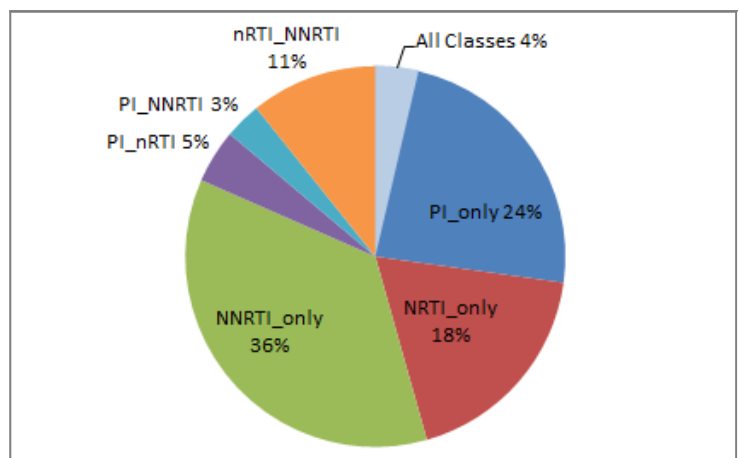
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transmitted to them at the time of their infection. Michigan, a moderate morbidity state of approximately 800 new HIV infections diagnosed annually, has rates of TDRM comparable to national rates for the three most common types of anti-retroviral drugs – protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). PI's interfere with the protease enzyme that HIV uses to produce infectious viral particles. NRTI's and NNRTI's both interfere with the step in the HIV life cycle where the enzyme reverse transcriptase converts HIV RNA to HIV DNA. NRTI's are faulty DNA building blocks that when incorporated into the newly forming HIV DNA produce a faulty chain that cannot maintain its integrity. NNRTI's bind to reverse transcriptase enzymes interfering with it's ability to convert the HIV RNA to HIV DNA. Beginning in 2014 MDHHS has also begun to look at emerging resistance to Integrase Inhibitors. Integrase Inhibitors terminate the spread of HIV by interfering with the ability of the newly created HIV DNA to be integrated with the CD4 cell's DNA. The next MHS report will include information regarding resistance to Integrase Inhibitors.

TDRM by Drug Class

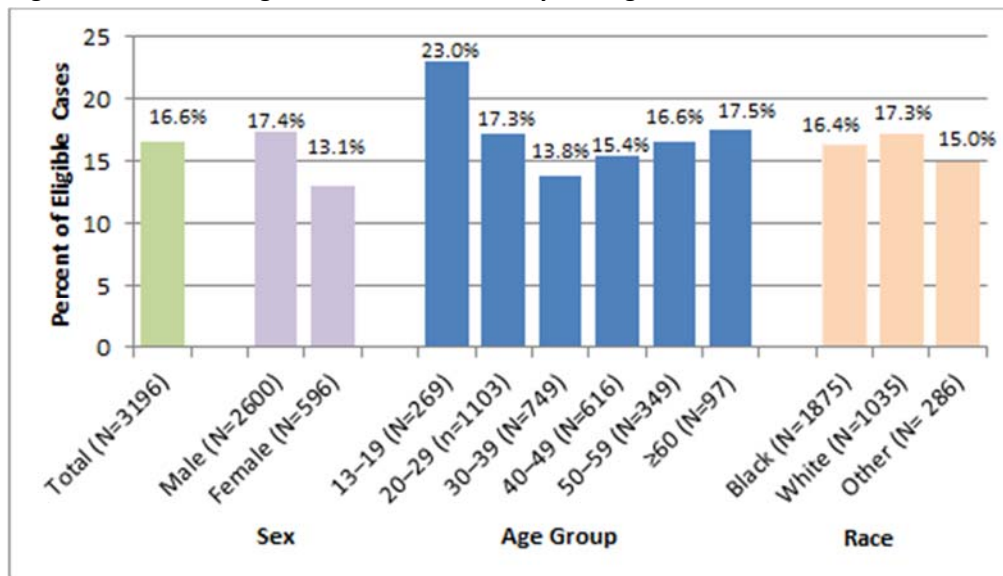
Of the 530 Michigan HIV cases with a genotype collected by MDHHS between 2004 and 2014 within 3 months of their diagnosis and exhibiting evidence of TDR, 78% had resistance to only 1 class of antiretroviral drugs. Among this 78%, PI, NRTI and NNRTI had rates ranging from 18%-36% of single drug class resistance with NNRTI-only comprising the largest portion (36%). 19% of the 530 cases had multi-class drug resistance with 4% of those cases exhibiting resistance to all three major classes of antiretrovirals used to treat HIV.

Figure 3: TDRM by Drug Class (N=530)



TDRM by Sex, Age, and Race

Figure 4: Percent of Eligible Cases with TDRM, by Sex, Age, and Race



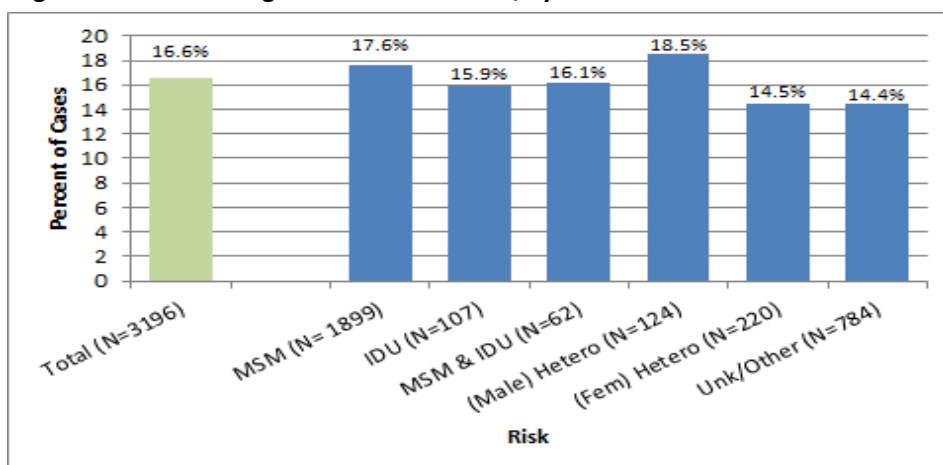
Females have a statistically lower percentage of TDRM compared to the percentage overall. Additionally, individuals within the 13-19 year old age group had the highest percentage of TDRM, which also was statistically significant. When considering race, all percentages of TDRM in the categories were comparable to that of the total population.

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TDRM by Risk

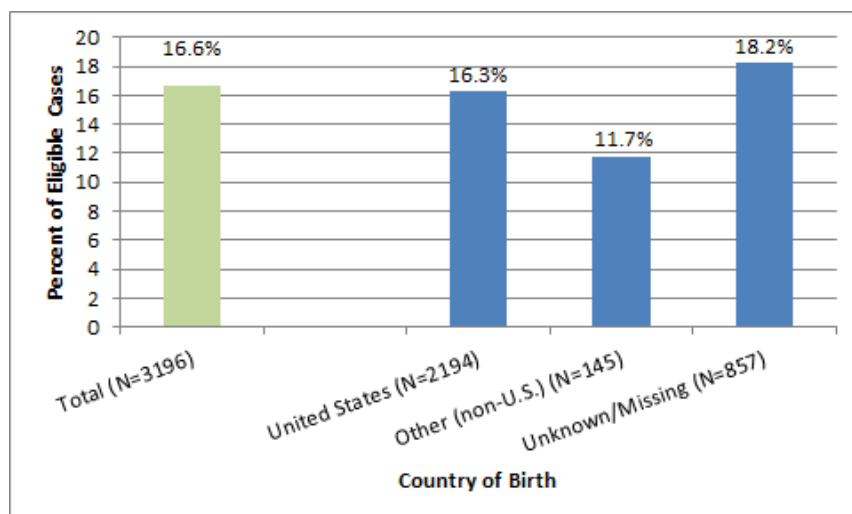
Among the new cases with an eligible genotype, males who had heterosexual contact with a high-risk or HIV positive female had the highest rate of TDRM, however this was not statistically significant. Other risk categories were comparable to the proportion of TDRM in the total eligible cases.

Figure 5: Percent of Eligible Cases with TDRM, by Risk



TDRM by Country of Birth and Residency at Diagnosis

Figure 6: Percent of Eligible Cases with TDRM, by Country of Birth



HIV-positive cases born outside of the U.S. had the lowest rate of TDRM. The 'Unk/Other' category of Residency at Diagnosis had the highest rate of TDRM. There was no statistically significant difference between the categories.

HIV Subtype or Circulating Recombinant Form

The HIV-1 group M (for Main) virus is the most common form of the HIV virus circulating in the world population. It is estimated that 90% of all infections world-wide are with HIV-1 group M and an even higher percentage is believed to represent the US population. HIV-1 group M is further divided into multiple subtypes. Subtype B is the most common form found in Europe, the Americas, Japan, Thailand, and Australia. It is estimated that up to 98% of all HIV infections in the US are HIV-1 group M subtype B. Subtype A is commonly found in West Africa; subtype C is often seen in Southern Africa, India, and Nepal; and subtype D is seen only in Eastern and central Africa¹. There are also circulating recombinant forms which represent recombination or exchange of genetic material between two HIV subtypes to create a new circulating form of HIV. All 7,802 Michigan cases with a genotype sequence collected by MDHHS from 1981-2014 were considered for subtype analysis. (Note that this is a different denominator than what has been represented in earlier figures.)

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Since subtype does not change over the course of an individual's infection we did not restrict this analysis to only those genotypes collected within the first 3 months following diagnosis).

Figure 7 shows the completeness of genotypes used for subtype analysis by year of diagnosis. Michigan's subtype analysis data spans a wide range of years in which cases were diagnosed, 1983-2014. This wide range helps to add to the generalizability of the data to all Michigan cases.

Figure 7: Genotype Completeness for Subtype Analysis in Michigan, 1983-2014

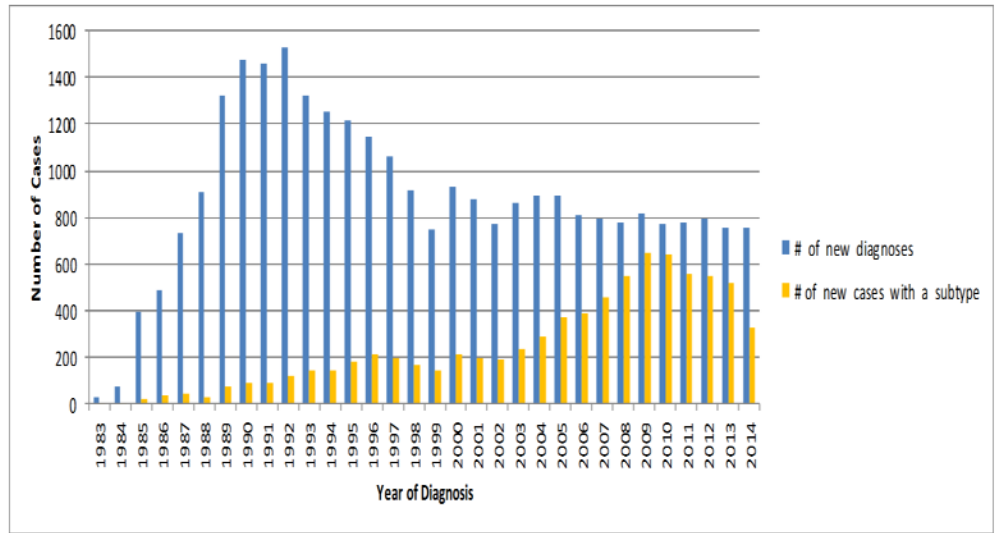


Figure 8: Subtype Category Proportions of Cases with a Valid Genotype in Michigan, diagnosed 1983-2014 (N= 7,802)

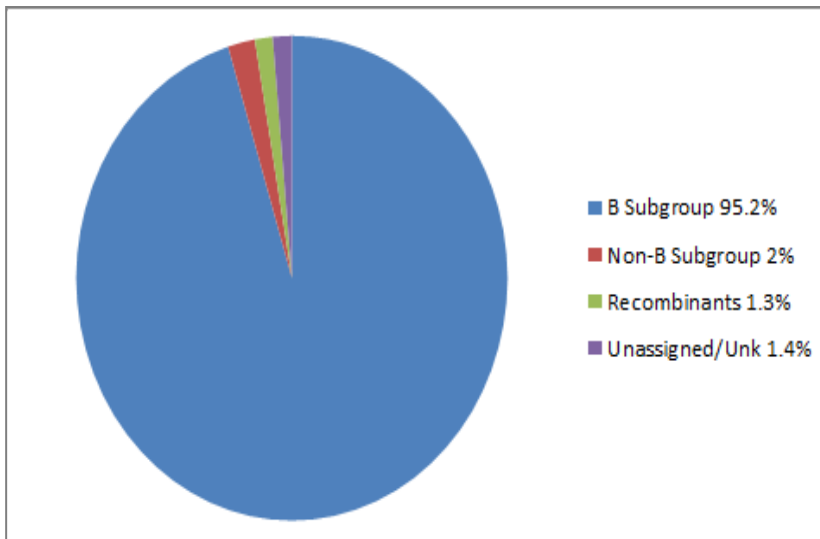
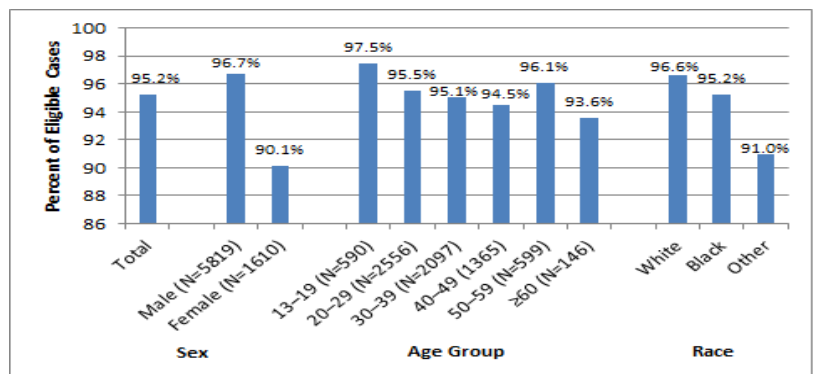


Figure 8 shows the subtype category proportions of all Michigan cases diagnosed 1983-2014 with a genotype sequence collected by MDHHS between 2004-2014 (n= 7,802). In Michigan, 95.2% of cases were subtype B. This mirrors the national rate of 96.2%. Other subtypes grouped together constituted only an additional 2% of the total, leaving 1.3% of Michigan cases with a genotype sequence as circulating recombinant forms and 1.4 as Unassigned or Unknown.

Figure 9 shows the distribution of HIV subtype B among genotyped Michigan cases by sex, age, and race. All demographic groups had significantly different strata from the total percentage. The lower percentage of females with a subtype B of HIV reflects the female, HIV-positive immigrant population who come from areas in the world where the main circulating form of the HIV virus is a non-B subtype. Young cases between the

Figure 9: Distribution of HIV subtype B by sex, age, and race for cases with a valid genotype, 1981-2014



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the ages of 13-19 years had a higher than expected percentage of HIV subtype B, while those aged 40-49 years had a lower than expected percentage. The 'Other' race group had a lower percentage with HIV subtype B than the other groups. Again, this is reflective of an immigrant population who come from areas in the world where the main circulating form of HIV is a non-B subtype.

Figure 10: Distribution of HIV non-B subtype by sex, age, and race for cases with a valid genotype, 1981-2014

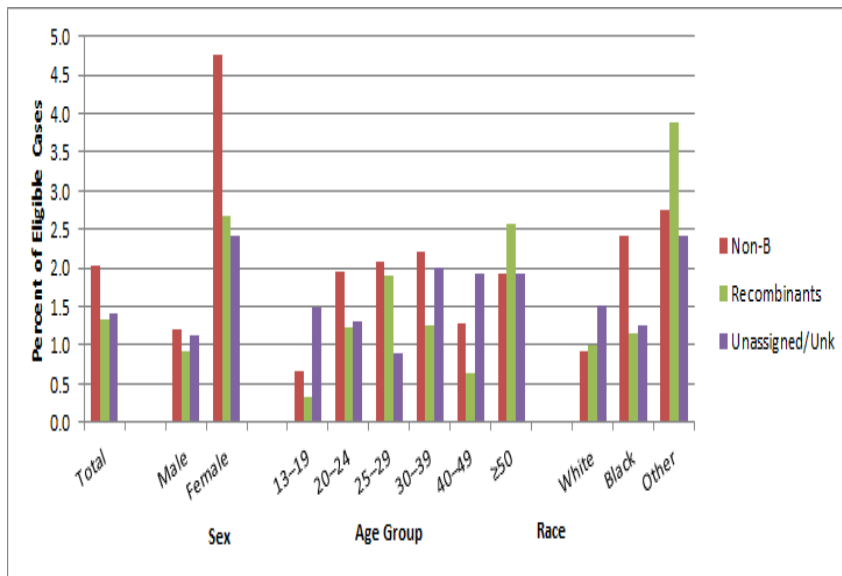
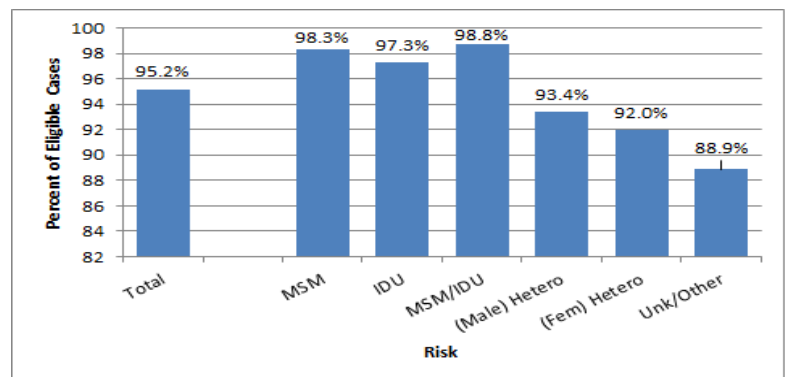


Figure 10 shows the distribution of non-B HIV subtypes among genotyped Michigan cases by sex, age at diagnosis group, and race. Non-B subtype HIV cases generally reflect immigrant persons and the distribution reflects the circulating HIV virus subtypes of the areas where they originally came from. Females and 'Other' race had a larger than expected percentage of HIV non-B subtype and recombinants. Those in the 30-39 age group had a larger than expected percentage of recombinants. Females also had a higher percentage of HIV where the subtype was unassigned or unknown

Figure 11 shows the distribution of HIV subtype B by risk. MSM had a larger than expected percentage of HIV subtype B, while Unknown/Other had a lower than expected percentage of HIV subtype B.

Figure 11: Distribution of HIV subtype B by Risk for cases with a valid genotype, 1981-2014



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Figure 12 shows the distribution of HIV non-B subtype by risk. The larger percentage of Male Heterosexual, Female Heterosexual, and Unknown/Other cases with a non-B subtype HIV virus reflects a larger proportion of immigrant cases who report these risks and come from areas in the world where non-B subtype is the main circulating form of HIV (such as Africa and Asia). Those with an Unknown or Other risk also had larger than expected percentage of recombinants and unassigned or unknown HIV.

Figure 12: Distribution of HIV non-B subtype by Risk for cases with a valid genotype, 1981-2014

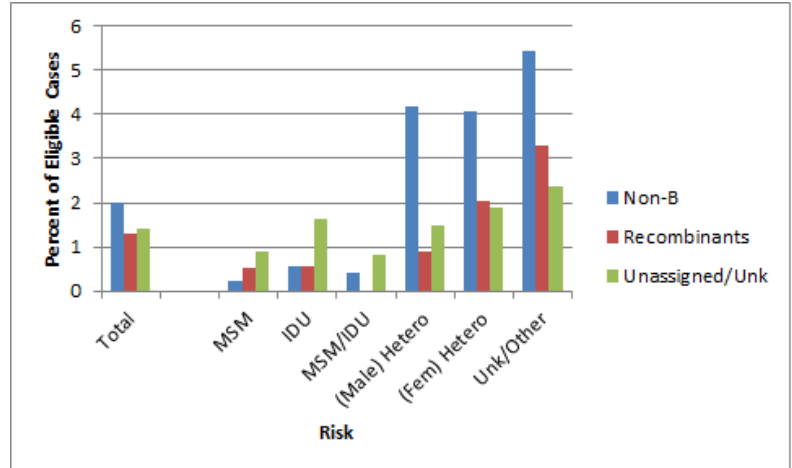


Figure 13: Distribution of Cases by Subtype and Country of Birth for cases with a valid genotype, 1981-2014

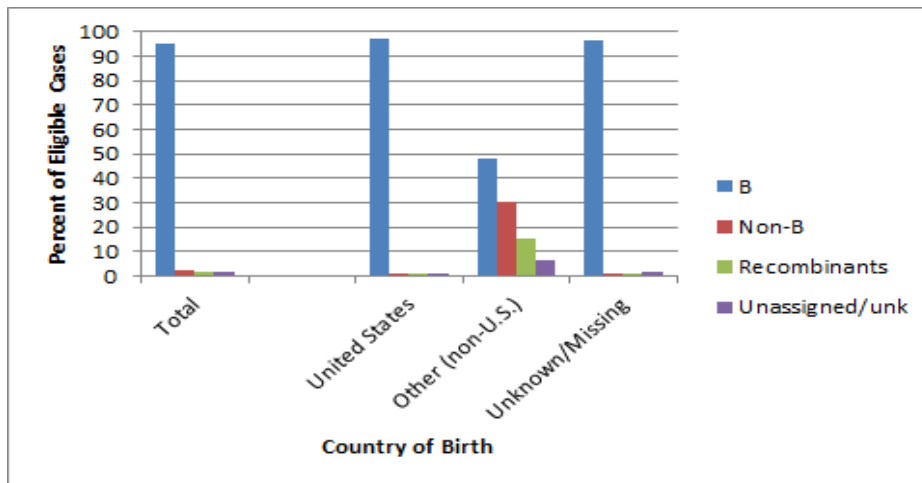


Figure 13 shows the distribution of case by subtype and country of birth. Note that slightly less than half (45.2%) of cases born outside of the United States are non-B subtype or recombinants. This is higher than the national average of 29.6% and is indicative of a higher immigration rate of people from areas of the world where non-B subtype HIV is

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