CROI 2016 Update
NEAETC, March 21, 2016

UNITED STATES EPIDEMIOLOGY
Estimating the lifetime risk of HIV in the United States (from NHSS*, census, mortality data, 2009-2013)

Hess K et al. CROI, Boston, 2016. abstract 52.

* National HIV Surveillance System
Estimating the lifetime risk of HIV in the United States 2009-2013

• Overall lifetime risk of HIV diagnosis in the U.S. Has decreased to 1:99 (from 2004-5 estimate of 1:78)

• Large disparities:
  – MSM most impacted group 1:6 all MSM
    • Highest risk, of 1:2, in black MSM
  – African Americans: most affected racial/ethnic group
    • 1:20 for men (1:132 for white men), 1:48 for women (1: 880 for white women) = x 18 fold in black women, when compared to white
  – People who inject drugs (PWID)
    • 1:23 women, 1:36 men; 1:6 black women, 1:9 black men
  – People living in the South
    • Washington, DC (1:13), Maryland (1:49), Georgia (1:51), Florida (1:54), and Louisiana (1:56).

• Limitations: HIV diagnosis and death rates used, not incidence, assuming diagnosis rates remain constant

Hess K et al. CROI, Boston, 2016. abstract 52.
Estimating the lifetime risk of HIV in the United States 2009-2013

Hess K et al. CROI, Boston, 2016. abstract 52.
The HIV Care Continuum and Treatment Cascade

HIV Care Continuum Shows Where Improvements are Needed

In the US, 1.2 million people are living with HIV. Of those:

- 86% Diagnosed
- 40% Engaged in care
- 37% Prescribed ART
- 30% Virally suppressed

Sources: CDC National HIV Surveillance System and Medical Monitoring Project, 2011.
Increasing Rates of Viral Suppression
United States 2009-2013

- HIV continuum: diagnosed → engaged → Prescribed ART → viral suppression
- Surveillance data through complex sampling in 23 jurisdictions (people in care)

![Graph showing increasing rates of viral suppression from 2009 to 2013](image)

*HIV-1 RNA < 200 c/mL at last test. †HIV-1 RNA < 200 c/mL at all tests from previous 12 mos.

Increasing Rates of Viral Suppression in the United States From 2009-2013

### Viral suppression at last test during past 12 months: Medical Monitoring Project, 2009–2013

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2013</th>
<th>( \beta ) trend*</th>
<th>change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
<td>%</td>
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<tr>
<td>Women</td>
<td>66</td>
<td>62 – 70</td>
<td>77</td>
<td>73 – 80</td>
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<tr>
<td>18–29 year olds</td>
<td>56</td>
<td>50 – 62</td>
<td>68</td>
<td>63 – 72</td>
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<tr>
<td>30–39 year olds</td>
<td>62</td>
<td>58 – 65</td>
<td>75</td>
<td>70 – 80</td>
</tr>
<tr>
<td>African Americans</td>
<td>64</td>
<td>61 – 68</td>
<td>76</td>
<td>72 – 79</td>
</tr>
<tr>
<td>Overall</td>
<td>72</td>
<td>69 – 74</td>
<td>80</td>
<td>78 – 83</td>
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### Sustained viral suppression during past 12 months: Medical Monitoring Project, 2009–2013

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<td>46 – 55</td>
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</tr>
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</table>

* \( P_{\text{trend}} \) for all coefficients <0.01

### Viral suppression

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<thead>
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<tbody>
<tr>
<td>MSM</td>
<td>76</td>
<td>82*</td>
<td>+8</td>
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### Sustained viral suppression

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<tbody>
<tr>
<td>MSM</td>
<td>61</td>
<td>71*</td>
<td>+10</td>
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HIV PREVENTION IN WOMEN
Dapivirine Vaginal Ring for HIV Prevention in Women

ASPIRE (MTN-020\textsuperscript{1,2}) & The Ring Study (IPM-027\textsuperscript{3})

- Disappointing results of some oral PrEP trials in African women, due to low adherence
- Longer acting drug delivery system desired:
  - Silicone elastomer vaginal matrix ring containing 25 mg of the NNRTI dapivirine; ring replaced every 4 wks in both trials
- Randomized, double-blind phase III trials
  - Primary endpoints: efficacy and safety
- jointly enrolled 4588 HIV-neg women
  - ASPIRE 629 women at 15 sites
  - Ring study 1959 at 7 sites

† Microbicides Trials Network (MTN)
‡ International Partnership for Microbicides (IPM)
Dapivirine Vaginal Ring for HIV Prevention in Women
ASPIRE (MTN-020\(^1,2\)) results

- Women enrolled in 15 sites at 4 countries. Average age 26. STIs were prevalent
- Retention was high, average follow up 1.6 years, max nearly 3y
- Adherence measured by plasma levels (>95 pg/mL) and residual ring drug levels (<23.5 mg)
  - 82% adequate Dapivirine detected in plasma
  - 84% adequate residual Dapivirine in ring
  - Some discordance (high residual, adequate level, suggesting use only before clinic visit)
- No significant safety issues

Dapivirine Vaginal Ring for HIV Prevention in Women
ASPIRE (MTN-020\textsuperscript{1,2}) results

- Placebo arm: >4% HIV acquisition rate
- Overall 27% reduction in HIV acquisition
  - 97 in placebo, 71 in ring arm
- When excluding sites with low adherence, 37% reduction
  - 85 in placebo, 54 in ring arm
- Magnitude of effect age related; adherence was indeed lower in younger group
- In those with HIV, ~10% NNRTI resistance in both ring and placebo arms

Cumulative Incidence of HIV-1 Infection

Dapivirine Vaginal Ring for HIV Prevention in Women
The Ring Study (IPM 027) results

- 2:1 randomization; a fixed two year follow-up
- Same plasma and ring levels used for adherence
- 82% retention rate; 83% of samples indicated adherence to ring
- 77 conversions for an incidence 4.1/100py (drug) and 6.1/100py (placebo): 31% reduction
  - 37% reduction > 21 yo
  - 15% reduction ≤ 21 yo
  - 8.2/100py HIV incidence for placebo arm
    - Adherence age-dependent (trend)
- NNRTI resistance in converters
  - 18% and 16% respectively

Dapivirine Vaginal Ring for HIV Prevention in Women

**ASPIRE (MTN-020\textsuperscript{1,2}) & The Ring Study (IPM-027\textsuperscript{3})**

**Efficacy results**

- Monthly vaginal ring can reduce HIV risk
- Adherence most important predictor of effect
- Reduced protection, and highest incidence observed in women <21 in Aspire

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ASPIRE\textsuperscript{[1,2]}: 15 Sites</th>
<th>ASPIRE\textsuperscript{[1,2]}: 13 Sites*</th>
<th>The Ring Study\textsuperscript{[3]}</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Dapivirine (n = 1308)</td>
<td>Placebo (n = 1306)</td>
<td>Dapivirine (n = 1198)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo (n = 1197)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Dapivirine (n = 1300)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo (n = 650)</td>
</tr>
<tr>
<td>HIV infections, n</td>
<td>71</td>
<td>97</td>
<td>54</td>
</tr>
<tr>
<td>HIV incidence (per 100 PYs)</td>
<td>3.3</td>
<td>4.5</td>
<td>2.8</td>
</tr>
<tr>
<td>HIV protection efficacy, %</td>
<td>27 (P = .046)</td>
<td>37 (P = .007)</td>
<td>31 (P = .040)</td>
</tr>
<tr>
<td>Among women older than 21 yrs</td>
<td>-</td>
<td>56 (P &lt; .001)</td>
<td>37 (P = .10)</td>
</tr>
</tbody>
</table>

REPRODUCTIVE HEALTH AND MTCT
IMPAACT P1026s: DTG in Pregnancy

- Open-label study of 21 pregnant women on DTG 50 mg QD
- PK assessed in 2nd, 3rd trimester, 3-12w postpartum, and in infants
- HIV-1 RNA ≤ 50 c/mL: 100%
- median gestational age at birth: 38.9 wks
- Results:
  - 9/18 infants HIV negative, 9/18 pending
  - DTG trough and AUC lower in 2nd, 3rd trimester vs
    - UGT1A1/CYP3A4 induction by progesterone
    - half-life > x2 higher in infants
  - 4 infants had hypoglycemia
  - Congenital anomalies in 4
    - Anomalous pulmonic venous return, polycystic R kidney/CF, chin tremor, filum terminale fibrolipoma and sacral dimple
- Antiretroviral Pregnancy Registry: 0/10 (1st trimester) and 1/18 (2nd or 3rd trimester) birth defects with DTG exposure

P1084s: Effect of ART and TDF During Pregnancy on Newborn Bone Mineral Content

- TDF is the preferred ARV in pregnancy in both DHHS and WHO guidelines
- P1084S randomized pregnant women to:
  - Bone mineral content was compared
  - 137-150 infants/children per arm, 15% had evaluable DEXA; all black African
  - Median age for mothers was higher and gestational age at birth lower for triple arm
  - Infant dexa at 0-21d of age presented

P1084s: Effect of ART and TDF During Pregnancy on Newborn Bone Mineral Content

- Lumbar spine BMC: no difference between the arms
- Whole body BMC: significantly lower in LPV/r arms vs ZDV (+ sdNVP + TDF/FTC tail); no significant difference whether on TDF
- Overall reassuring results for TDF but both triple arms used r/LPV (limiting ability to assess EFV regimens), and regimens started at or after 28 weeks

<table>
<thead>
<tr>
<th>Whole Body BMC Comparison</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
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<tbody>
<tr>
<td></td>
<td>Mean Difference, g</td>
<td>P Value</td>
</tr>
<tr>
<td>LPV/RTV + ZDV/3TC vs LPV/RTV + TDF/FTC</td>
<td>+1.76</td>
<td>.41</td>
</tr>
<tr>
<td>ZDV (+ sdNVP + TDF/FTC tail) vs LPV/RTV + TDF/FTC</td>
<td>+9.73</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>ZDV (+ sdNVP + TDF/FTC tail) vs LPV/RTV + ZDV/3TC</td>
<td>+7.97</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Hormonal Contraceptive Implants and Efavirenz

- Efavirenz substantially reduces levels of levonorgestrel, a component of contraceptive implants
  - Prior pK study in Uganda: LNG 40 -54% lower when used with EFV (1)
  - variations in CYP2B6 likely account for the lower LVG pk (2)
- In Swaziland, 12.4% (15) of women taking efavirenz (EFV) while using the Jadelle implant became pregnant (3)
- All women using hormonal contraceptive implants (HCI) in an HIV clinic in Tororo, Uganda were studied
  - 148 HCI users: 62 (41.9%) on EFV-ART & 86 (58.1%) on a non EFV ART
  - Of the 148 women 9 (6.1%) conceived
  - All who conceived were on EFV; none of the women on conceived (p=0.0003)
  - For women who conceived, median duration between placement and pregnancy: 22.6 months
  - This strengthens evidence that in some women on EFV-based regimens HCI contraception may be ineffective

2. Nari M et al. CROI Boston 2016. abstrat 444
3. Perry et al, 2014
4. Okoboi et al. CROI Boston 2016. abstract 862
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OTHER COMPLICATIONS IN WOMEN
Stroke Incidence in the ALLRT Cohort 1998-2011

- ALLRT: longitudinal follow-up of patients enrolled in several ACTG treatment trials
- Stroke incidence and risk factors in patients who never had a stroke were evaluated
- 6933 patients followed
  - 20% women, >50% non-white
  - Median CD4 243 when starting ART
- 54 observed strokes in 32,023 person years

Chow F et al. CROI Boston 2016 43
HIV infected Women, African Americans, have a higher risk of stroke

- Highest rate of stroke was observed in black participants
- Women had a higher incidence of stroke (x2.88) than men
  - Driven by 40-49 YO women
- Being non-black was protective
- Being overweight was protective
- CD4<200, detectable VL, at the time of the stroke, increased risk
- Detectable VL at the time of stroke strongest risk factor (higher than traditional risk factors (e.g LDL, smoking, HTN)

Chow F et al. CROI Boston 2016 43
Multivariate model, based on findings for stroke risk at IV

![Adjusted relative risk of stroke/TIA graph]

- **Variable**: Sex (vs M), Race/Ethnicity (vs Black), Current age, Time-varying LDL, Time-varying hypertension, Time-varying BMI, Time-varying HIV RNA, Time-varying diabetes history, Smoking history, Time-varying renal dysfunction history
- **Relative Risk and 95% CI**
  - **Sex (vs M)**: F (1.59), M (0.95)
  - **Race/Ethnicity (vs Black)**: Hispanic + Other (0.42), White (0.85)
  - **Current age**: Every 10 years older (2.10)
  - **Time-varying LDL**: <160 (1.00), >=160 (2.54)
  - **Time-varying hypertension**: Yes (2.79)
  - **Time-varying BMI**: Underweight/Normal (0.46), Overweight/Obesity (1.00)
  - **Time-varying HIV RNA**: <=200 (1.00), >200 (3.10)
  - **Time-varying diabetes history**: Yes (1.68)
  - **Smoking history (vs No)**: Yes (1.63)
  - **Time-varying renal dysfunction history**: Yes (1.91)
QUESTIONS AND ASSESSMENT
Which of these statements about lifetime risk of HIV in the US is INCORRECT

A. Men who inject drugs have a higher lifetime risk than women who inject drugs
B. The highest lifetime risk of HIV is in black MSM
C. Lifetime risk of HIV in the US is higher in men than in women
D. Asian men have a lower lifetime HIV risk than white men
E. Lifetime risk of HIV is higher in Southern states when compared to the national risk
Dapivirine Ring Study
Which of the following statements is CORRECT

A. Dapivirine is a long-acting integrase-inhibitor used for HIV prevention in a vaginal matrix ring delivery system
B. Dapivirine ring was less effective in reducing HIV acquisition among women 21 year-old or younger
C. In the ASPIRE study there was excellent correlation between plasma drug levels and residual ring drug levels, the two parameters used to measure adherence
D. Among HIV seroconverters, drug resistance rates were significantly lower in the placebo arm