Prophylaxis for herpes zoster among HIV-positive persons

OI Updates

Ruanne V Barnabas, MBChB, DPhil
Global Health and Medicine, University of Washington

Outline

- Background
- Methods
- Results
- Conclusions
- DHHS Guidelines
- Summary

The Journal of Infectious Diseases

BRIEF REPORT

Acyclovir Prophylaxis Reduces the Incidence of Herpes Zoster Among HIV-Infected Individuals: Results of a Randomized Clinical Trial

Ruanne V. Barnabas,[1,2,3,6] Jared M. Baeten,[1,2,3] Jairam R. Lingappa,[1,2] Katherine K. Thomas,[1] James P. Hughes,[4,6] Nelly R. Mugo,[1] Sinead Delany-Moretlwe,[7] Glenda Gray,[9] Helen Rees,[7] Andrew Mujugira,[1,3] Allan Ronald,[10] Wendy Stevens,[8] Saidi Kapiga,[11] Anna Wald,[1,2,5,6] and Connie Celum[1,2,3]; for the Partners in Prevention HSV/HIV Transmission Study Team

Departments of [1]Global Health, [2]Medicine, [3]Epidemiology, [4]Biostatistics, [5]Laboratory Medicine, University of Washington, and [6]Vaccine and Infectious Diseases Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; [7]Wits Reproductive Health and HIV Institute, and [8]Department of Molecular Medicine and Haematology, University of Witwatersrand, Johannesburg, [9]Perinatal HIV Research Unit, Soweto, South Africa; [10]Department of Medicine, University of Manitoba, Winnipeg, Canada; and [11]Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, United Kingdom

DHHS: Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV Infected Adults and Adolescents

Background

- The risk for herpes zoster is 12-to-17 fold higher among HIV-positive persons compared to HIV-negative individuals and remains 2-3 fold higher even after initiation of antiretroviral therapy.
- An observational study among 39 AIDS patients found that high dose acyclovir (2.4 g daily) reduced zoster recurrence at 12 months by 68%.
- Evidence for herpes zoster prophylaxis among HIV-positive individuals is limited.
- We hypothesized that daily acyclovir prophylaxis would reduce the incidence of herpes zoster among HIV-positive individuals.

Methods

- Data were from the Partners in Prevention HSV/HIV Transmission Study, a randomized, double-blind, placebo-controlled trial of acyclovir (400 mg twice daily), among HIV-infected women and men from 7 African countries.
- At baseline, none of the participants were receiving antiretroviral therapy and all had CD4 counts >250 cells/μL.
- At quarterly visits over 24 months, zoster episodes reported since the last study visit and observed on skin examination were recorded.
- We used survival analysis to estimate the effect of acyclovir prophylaxis on herpes zoster incidence in the acyclovir arm compared to the placebo arm.
- Data were not censored at antiretroviral therapy initiation.
- We analyzed all zoster episodes in an individual and used a robust variance to control for correlation due to multiple events per person.

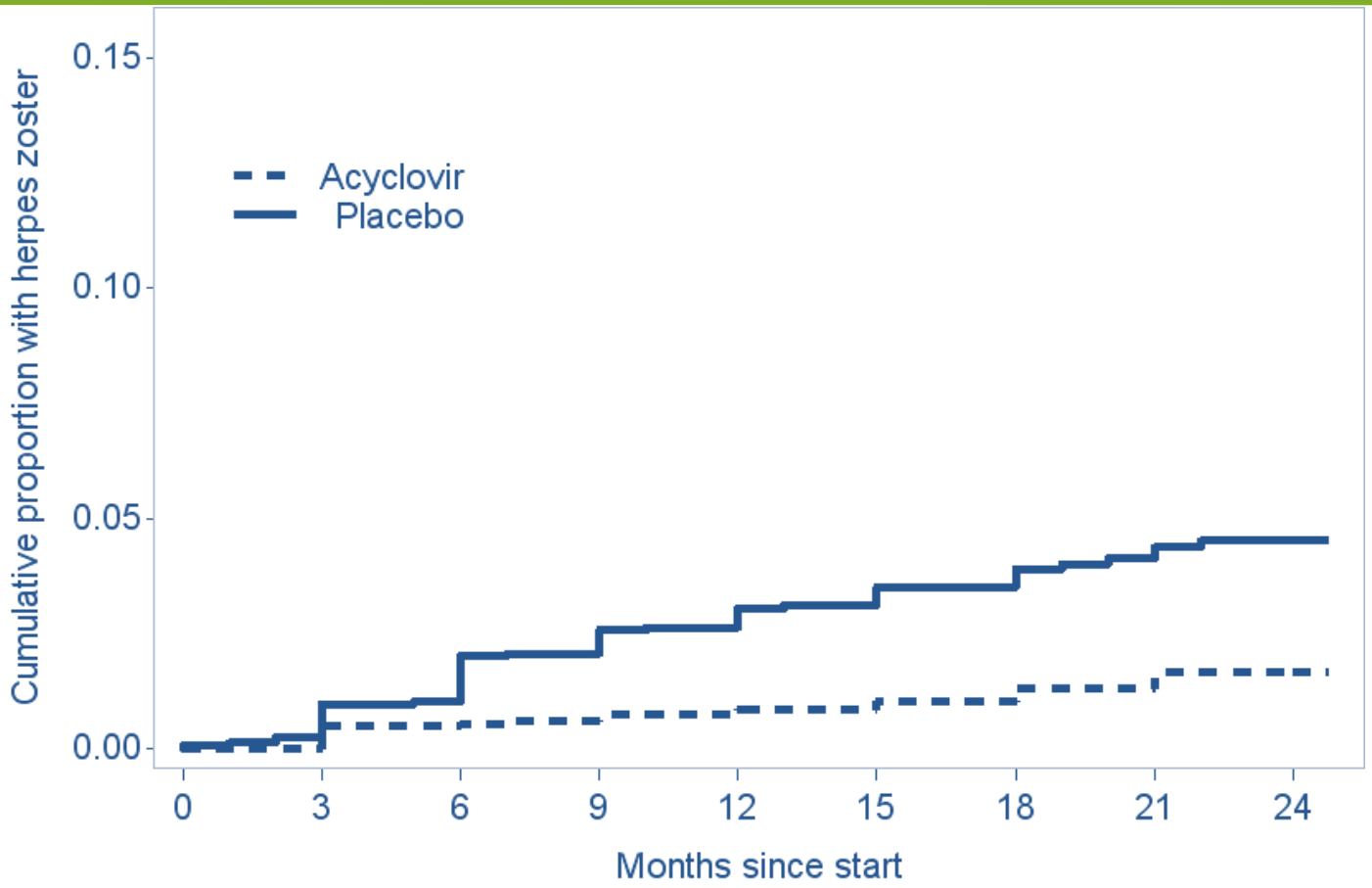
Results

- Of the 3,381 HIV-infected participants, 1,693 were randomized to acyclovir and 1,688 to placebo. There were no significant differences between baseline characteristics of the two groups.
- One hundred reports of herpes zoster were received during follow-up, of which 20 were observed by skin examination only, 66 were self-reported as occurring between study visits, and 14 were observed and reported.
- Of these 100 herpes zoster events, 26 occurred in the acyclovir arm versus 74 in the placebo arm (placebo arm incidence 2.88 per 100 person-years).
- Overall, acyclovir prophylaxis decreased the incidence of herpes zoster by 65% in the acyclovir arm compared to the placebo arm (HR = 0.35, 95% CI 0.20-0.63, $p<0.001$).

Results: Baseline characteristics

Characteristic	Acyclovir N (%) (N= 1693)	Placebo N (%) (N= 1688)
Female	1132	1152
Age, median (IQR)	32 (27-38)	32 (26-38)
CD4, median, cells/mm^3 (IQR)	470 (350-637)	454 (343-625)
HIV-1 plasma RNA, median, $\log_{10}$ copies/mL (IQR)	4.1 (3.4-4.7)	4.1 (3.3-4.7)
HIV-1-associated symptoms		
Weight loss >10%, prior year	83 (5%)	68 (4%)
Fever >1 month, prior year	56 (3%)	71 (4%)
Diarrhea >1 month, prior year	10 (1%)	19 (1%)
Cough >1 month, prior year	87 (5%)	110 (7%)
Genital ulcers, prior 3 months	387 (23%)	376 (22%)
Clinical diagnoses, by self-report		
Pneumonia, prior year	78 (5%)	67 (4%)
Tuberculosis, prior year	53 (3%)	68 (4%)
Herpes zoster, prior year	66 (4%)	64 (4%)
Physical examination findings		
Lymphadenopathy	240 (15%)	256 (15%)
Oral candidiasis	8 (0%)	6 (0%)
Herpes zoster	21 (1%)	18 (1%)
GUD	50 (3%)	47 (3%)

Results: Herpes zoster by treatment arm



No. at risk									
Placebo	1665	1665	1642	1608	1484	1286	1056	816	616
Acyclovir	1659	1656	1621	1562	1421	1219	1000	789	607

Incidence by treatment arms

	Acyclovir	Placebo		
	# events	# events	Hazard Ratio (95% CI)	P value
All zoster events^	26	74	0.35 (0.20-0.63)	<0.001
Zoster observed on exam	12	22	0.58 (0.20-1.62)	0.29
Report of zoster	16	64	0.25 (0.14-0.43)	<0.001

Incidence by subgroup

Subgroups	Acyclovir	Placebo		
	# events	# events	Hazard Ratio (95% CI)	P value (Test effect modification)
Gender				
Male	10	30	0.31 (0.15-0.66)	
Female	16	44	0.38 (0.17-0.85)	0.77
Age				
< 30 years	13	29	0.46 (0.24-1.24)	
≥30 years	13	45	0.29 (0.16-0.54)	0.45
CD4 count				
< 350	8	36	0.26 (0.12-0.57)	
≥ 350	18	38	0.46 (0.22-0.97)	0.26
Viral load				
< 10,000	6	17	0.37 (0.15-0.93)	
10,000-99,999	12	30	0.41 (0.15-1.09)	
≥100,000	8	27	0.26 (0.11-0.62)	0.78
Post randomization				
ART use in prior period				
Yes	0	6	0.00 (0.00-1.06)*	
No	26	68	0.38 (0.22-0.69)	-
Temporal modification of effect				
<12 months since randomization	14	50	0.29 (0.14-0.58)	
≥12 months since randomization	12	24	0.50 (0.24-1.03)	0.23

Results

- This effect was not modified by gender, age (<30 years and ≥30 years), CD4 count (<350 and ≥350 cells/μL) or plasma HIV viral load (<10,000; 10,000-99,999; ≥100,000 copies/mL).
- There was no temporal change in acyclovir effect; comparing the effect in the first 12 months of the study with the second 12 months. (p=0.23).
- Six cases of herpes zoster occurred among participants who initiated antiretroviral therapy; all were in the placebo arm.
- For the 6 participants on ART in the placebo arm, who developed herpes zoster, the range of days on ART at first zoster report was 3 days to 77 days.
- We did not observe an impact of ART on herpes zoster incidence, but the number of participants on ART was small (124 person-years at risk in the acyclovir group and 155 person-years at risk in the placebo group).

Discussion

- Acyclovir prophylaxis substantially reduced herpes zoster incidence among HIV-infected individuals by 65%, and was not modified by gender, age, CD4 count, plasma viral load or ART use.
- Other studies have found an increased incidence of zoster with declining CD4 count suggesting that acyclovir prophylaxis for herpes zoster could be targeted to HIV-positive persons with a CD4 count of ≤200 cells/μL who have not been previously vaccinated against zoster.
- Acyclovir prophylaxis also reduced GUD by 73%.
- Immunosuppressed persons, including transplant recipients, who receive antiviral prophylaxis against cytomegalovirus (CMV) or HSV with valganciclovir, ganciclovir, valacyclovir, or acyclovir have a lower risk of herpes zoster.
- Herpes zoster is a cause of considerable morbidity among HIV-positive individuals, therefore clinical guidelines for HIV care should consider acyclovir prophylaxis.

Summary

- We estimated the effect of acyclovir prophylaxis (400mg twice daily) on herpes zoster incidence among 3,381 HIV-infected person, of whom 1,693 were randomized to acyclovir and 1,688 were randomized to placebo.
- Over 24 months, **acyclovir prophylaxis reduced herpes zoster incidence by 65%** (HR = 0.35, 95% CI 0.20-0.63, p<0.001); the effect was not modified by gender, age, CD4 count, HIV viral load or ART use.
- Clinical guidelines for HIV care should consider acyclovir prophylaxis to prevent herpes zoster particular for the first six months following ART initiation.

DHHS Guidelines

- HIV-positive persons without evidence of varicella immunity
  - Avoid exposure
  - Vaccinate household members without immunity
  - Post-exposure prophylaxis (VZV-IG – IND or IVIG)
  - Short term PEP with acyclovir/valacyclovir starting 7-10 days after exposure
  - Varicella vaccination
    - Recommended for children and with CD4 > 15%
    - Consider for adults with CD4 count >200 cells/µL – treat vaccine caused disease (rare)

- Long term prophylaxis with acyclovir to prevent herpes zoster recurrences is not routinely recommended

DHHS: Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV Infected Adults and Adolescents

Vaccination guidelines

- Varicella vaccination (prevent primary infection) recommended for:
  - born in 1980 or after and have not gotten two doses of this vaccine
  - do not have immunity to this disease and CD4>200 cells/µL

- Zoster vaccination
  - Recommended for persons age 60 or older and not severely immunocompromised
  - CD4 count >200 cells/µL

- Herpes zoster is **not** an indication to delay ART initiation – risk for IRIS (2-4 fold increase in VZV reactivation)

DHHS: Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV Infected Adults and Adolescents

Special considerations during pregnancy

- HIV+ pregnancy women who are susceptible to VZV, who have close contact with active varicella or herpes zoster should receive VZV IG (VariIG) asap (within 10 days)
- If acyclovir PEP is provided, conduct VZV serology
- Pregnancy is a CI to the varicella vaccination and the herpes zoster vaccination

Thank you

rbarnaba@uw.edu

- **Partners PrEP Study Team**
- **Sites:**
  - Eldoret, Kenya (Moi U, Indiana U): Edwin Were (PI), Ken Fife (PI), Cosmas Apaka
  - Jinja, Uganda (Makarere U, UW); Patrick Ndase (PI), Elly Katabira (PI), Fridah Gabona
  - Kabwohe, Uganda (KCRC): Elioda Tumwesigye (PI), Rogers Twesigye
  - Kampala, Uganda (Makarere U): Elly Katabira (PI), Allan Ronald (PI), Edith Nakku-Joloba
  - Kisumu, Kenya (KEMRI, UCSF): Elizabeth Bukusi (PI), Craig Cohen (PI), Josephine Odoyo
  - Mbale, Uganda (TASO, CDC): Jonathan Wangisi (PI), Akasiima Mucunguzi
  - Nairobi, Kenya (KNH/U Nairobi, UW): James Kiarie (PI), Carey Farquhar (PI), Grace John-Stewart (PI), Harrison Tamooh
  - Thika, Kenya (KNH/U Nairobi, UW): Nelly Mugo (PI), Kenneth Ngure
  - Tororo, Uganda (CDC, TASO): Jim Campbell (PI), Jordan Tappero (PI), Aloysious Kakia

- **University of Washington Coordinating Center:**
  Connie Celum (PI and Co-Chair), Jared Baeten (Co-Chair and Medical Director), Deborah Donnell (Statistician), Justin Brantley, Robert Coombs, Carlos Flores, Lisa Frenkel, Harald Haugen, Ting Hong, Jim Hughes, Erin Kahle, Becky Karschney, Lara Kidoguchi, Meighan Krows, Jai Lingappa, Toni Maddox, Angela McKay, Julie McElrath, Allison Mobley, Susan Morrison, Kelly Moutsos, Apollo Odika, Hilda O'Hara, Dana Panteleeff, Marothodi Semenya, John Sparkman, Katherine Thomas
- **Adherence Ancillary Study:** David Bangsberg, Jessica Haberer, Norma Ware, Monique Wyatt, Steve Safren, Christina Psaros, Craig Hendrix, Namandjé Bumpus
- **DF/Net** (data center)**: Lisa Ondrejcek, Darryl Pahl, Jae Chong**
- **CLS** (laboratory oversight): **Wendy Stevens, Charlotte Ingram, Ute Jentsch, Mukthar Kader, Nombulelo Gqomane, Feroza Bulbulia, Jan van den Heuvel**
- **ClinPhone/Perceptive Informatics** (randomization)
- **Gilead** (study drug donation)**: Jim Rooney**
- **Bill & Melinda Gates Foundation** (study funder)**: Stephen Becker**
- **UW CFAR Clinical Retrovirology Core (P30-AI-027757)**
- **HIV serodiscordant couples who tested, screened, & participated**