Association Between Cytomegalovirus Viremia and Incident Retinitis, Progression of Existing Lesions, and Reactivation in HIV+ Patients in the U.S.

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Presentation overview

1. Introduction to CMV, retinitis, and viremia
2. Our hypothesis
3. The LSOCA dataset
4. Methods & development of risk sets
5. Analysis
6. Limitations and next steps

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Cytomegalovirus overview

- Cytomegalovirus (CMV), the largest member of the herpes virus family, infects people of all ages
- 1 out of every 200 babies are born with a congenital CMV infection
- Over half of adults have been infected by age 40
- Most people infected with CMV present no signs or symptoms
- Past exposure and latent infection can be detected with blood tests; use **Immunoglobulin G (IgG)** and Immunoglobulin M (IgM) values
- Best known to infect and/or reactivate in severely immunocompromised humans such as organ transplant recipients and **those living with HIV/AIDS**

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CMV retinitis overview

- **Cytomegalovirus retinitis (CMVR)** is the most common ocular opportunistic infection associated with AIDS, and is becoming a major cause of blindness in regions of the world most affected by HIV/AIDS (Africa, SE Asia)
- CMVR begins with floaters, causing blind spots and blurred vision; eventually retinal lesions develop
- CMVR will become bilateral (affecting both eyes) in 80% of cases if left untreated, and eventually results in a destroyed retina and optic nerve, causing irreversible blindness
- Incidence of CMVR has been declining in recent years related to the increased use of highly active anti-retroviral therapy (HAART)

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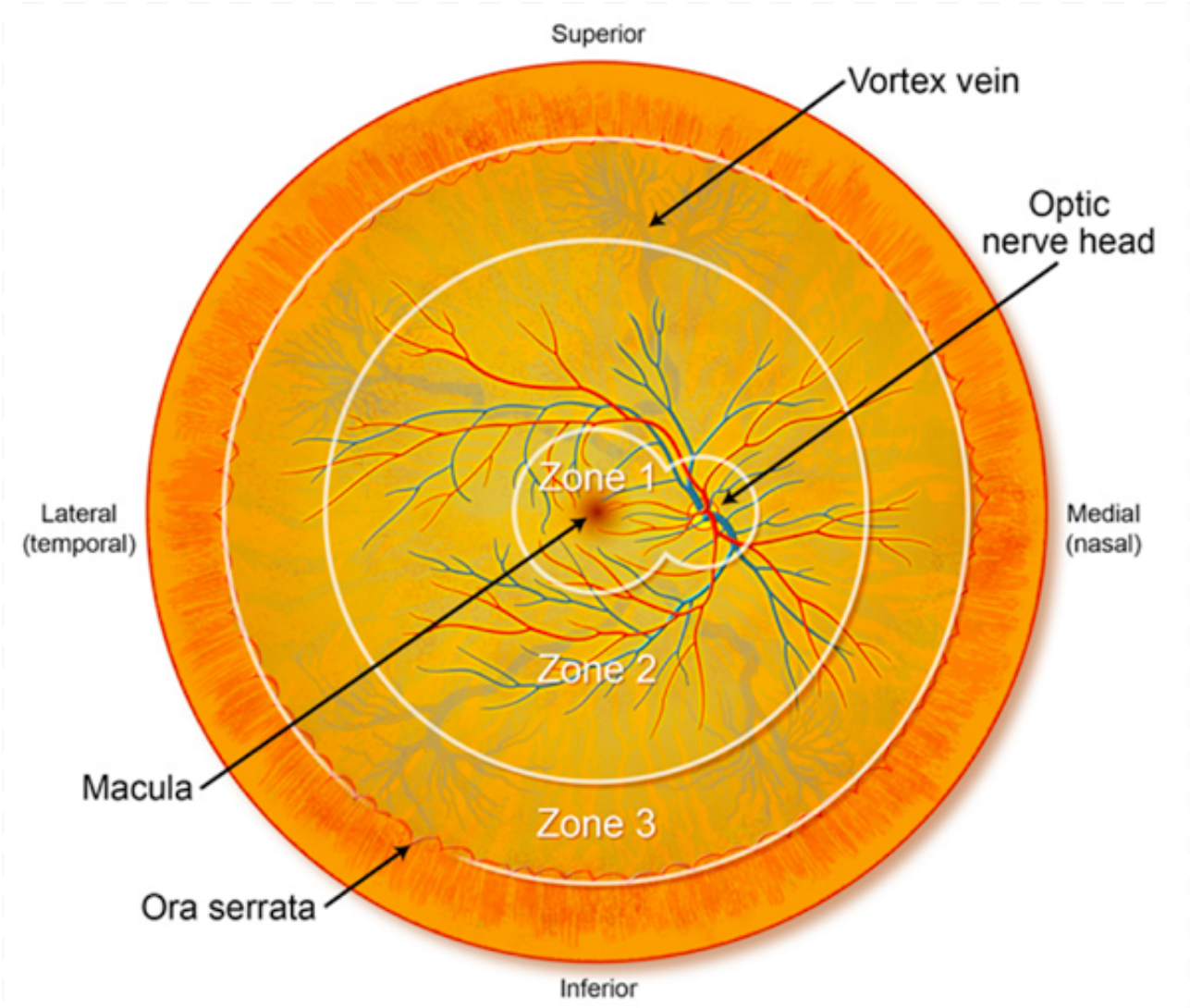
The eye



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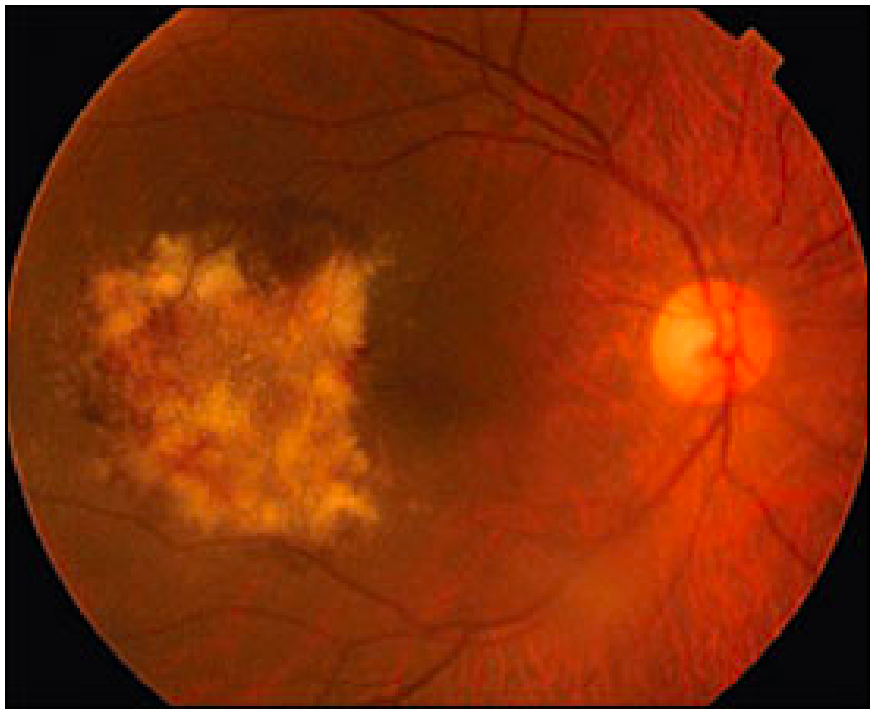
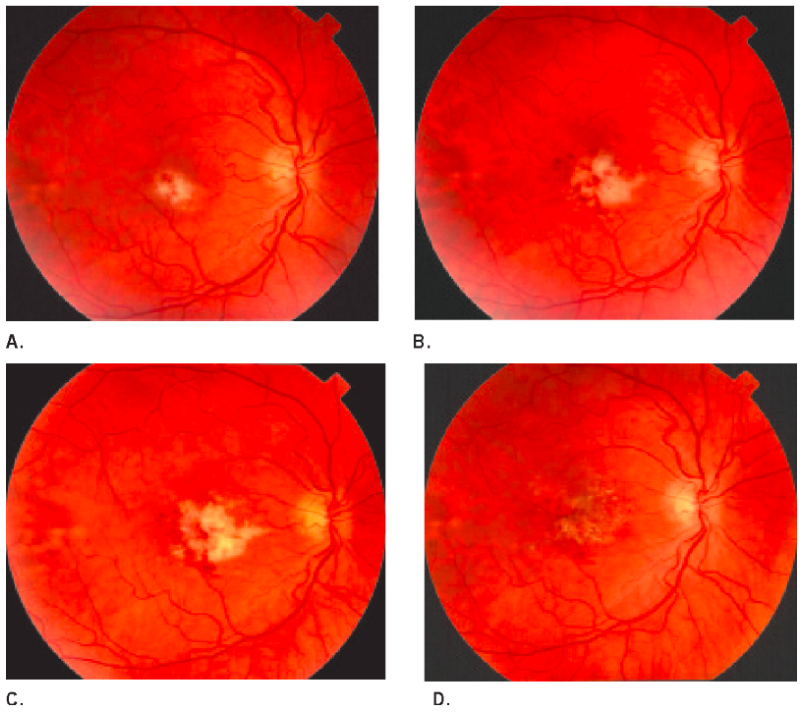
Retinitis shown in fundus photographs





CMVR usually affects the peripheral retina (zones 2 and 3, mid- and far periphery) (left). Other less common types include macular CMVR (zone 1, back of the eye) (right).

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CMV viremia overview

- **CMV viremia** is a more precise quantifier of the virus' activity because it indicates **active** rather than latent CMV infection; virological markers of ongoing CMV replication are likely to be more accurate predictors of retinitis activity
- In CMV seropositive patients with AIDS, detection of CMV viremia has been shown to be predictive of death and provides prognostic information in addition to CD4 counts and HIV viral load
- Research into the utility of CMV viremia to predict CMVR onset and relapse as well as extra-ocular disease has seen mixed results
- Our work may be a potential tool to triage individuals at highest risk of ocular complications and blindness in resource limited settings

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Hypothesis

Via Dr. Gary Holland:

- CMV viremia (in the past 12 months) predicts incident disease or new/additional lesions (one of the criteria for progression, the other being border advancement of existing lesions)
- However, CMV viremia (in the past 12 months) is not associated with progression defined solely by enlargement of lesions (border advancement)

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LSOCA data

- The Longitudinal Study of Ocular Complications of AIDS (LSOCA) was a prospective observational study of patients with AIDS sponsored by Johns Hopkins and the National Eye Institute (NEI)
- 2392 U.S.-based patients 13+ years old with a prior diagnosis of AIDS with or without ocular complications were enrolled over a 4 year period
- Followup visits for patients without ocular complications happen every 6 months; if patient has ocular complications at baseline or is diagnosed during followup, followups occur every 3 months

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Subset of LSOCA data

- **Our subset** has n=1763: all patients who had at least one study visit as of 8/1/2004 whether they had viremia data or not (viremia data stopped as of 8/1/2003)
- I was given two datasets:
  - **reading center specific dataset (FPRC)** which is visit-eye specific - all activity, movement, and new lesion variables
  - **non-reading center specific dataset (noFPRC)** which is only visit-specific - all CD4, CD8, VL count, viremia, therapy variables - no eye-specific information
- Merged, calibrated, cleaned, made new variables that combine zone 1 and zone 2/3,...

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Basic descriptives

- n=1763, 9 with no FPRC data
- Mean 6 visits per patient, median 5, IQR 3-8, min 1, max 22
- 1269/1763 patients have ≥ 1 visit at which eye information is unknown; 1752/1763 patients have known eye info at baseline
- 281/1763 underwent IV therapy (drug) at ≥ 1 visit
- 31/1763 underwent local therapy (per-eye injection or implant) at ≥ 1 visit

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Frequency of events stratified by zone

	Zone 1	Zone 2/3	All zones
New lesion relative to previous visit			
Yes	11	32	32
No	1677	1656	1656
N/A	75	75	75
Most severe CMVR activity achieved			
None	1558	1365	1371
Inactive	123	241	239
Mild	29	54	56
Severe	41	85	85
N/A	12	18	12
Max border advancement, microns			
No movement	1652	1616	1610
< 750	10	16	17
[750, 1500)	10	6	9
[1500, 3000)	4	11	11
≥ 3000	12	39	41
N/A	75	75	75

Table 1. Frequency of events throughout study stratified by zone

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CMVR status stratified by number of positive PCR tests for viremia

+ viremia tests	CMVR+	CMVR-	N/A	Total
0	270	1202	7	1479
>0	71	44	0	115
1	*46*	*39*	*0*	*85*
2	*18*	*4*	*0*	*22*
3	*5*	*1*	*0*	*6*
4	*1*	*0*	*0*	*1*
5	*1*	*0*	*0*	*1*
N/A	25	142	2	169
Total	366	1388	9	1763

Table 2. Patients with and without CMVR stratified by number of positive PCR tests for viremia

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General method

- We are only interested in viremia in the past year relative to a visit, so once a risk set is determined, an R function iterates through each patient and visit and creates a new data frame
- This allows us to look at only the visits of interest in a one year window into the past, detecting presence of any positive tests for CMV viremia and creating new variables to input into regression models

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Risk sets

A **risk set** is a subset of patients/visits that are at risk for an event.

Need to determine all those who are at risk to develop CMVR:

- When is a patient CMV+ at BL (no IgG data at followups)?
  - IgG $\geq$ 1.2 IU/mL
- Those who get CMVR at some point in the study should be assumed CMV+ regardless of their status at BL
- Those who are confirmed to be CMV- at BL and develop CMVR later should also be included - IgG test was either a false negative or the patient attained CMV at some point post-baseline and before the first CMVR lesion manifested

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Incident disease risk set

- The union of confirmed IgG+ patients and CMVR+ patients is the starting place for the incident CMVR risk set
  - 366 patients get CMVR at some point in the study
  - 1173 patients are IgG+ at baseline based on the 1.2 threshold (whereas 50 are IgG- at baseline, 3 of whom get CMVR later)
  - 1269 patients are in the risk set
- Additional constraint: the risk set needs to include only the 1407 patients who have no activity at baseline (no active or inactive lesions)
- The intersection of these two groups is **924 patients**
- Visits are removed with an unknown new lesion measure or that occur after incident disease occurs - 868 patients remain
- Visits are removed that have zero tests for viremia in the past year - **768 patients** remain

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Visits at risk for incident disease

	Viremia in the previous year		
Incident CMVR	No	Yes	Unknown
No	1202	34	172
Yes	5	6	1

Table 3. Visits at risk for incident CMVR stratified by viremia status in the year previous

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Additional lesions risk set

- Include the 340 patients who have had one or more CMVR lesions in the past (those who have inactive or active lesions at baseline)
- 12 patients had incident disease within the study, as shown by the previous analysis
  - 10 of these patients had visits after the incident disease occurred
  - 2 patients had the incident disease in their last followup
- Visits from **350 patients** are considered in this analysis
- Visits are removed with an unknown new lesion measure - 348 patients remain
- Visits are removed that have zero tests in the past year - **323 patients** remain

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Visits/eyes at risk for additional disease

	Viremia in the previous year		
Additional lesions	No	Yes	Unknown
No	2356	184	339
Yes	16	11	0

Table 4. Visits at risk for additional CMVR lesions stratified by viremia status in the year previous

	Viremia in the previous year		
Additional lesions	No	Yes	Unknown
No	4479	338	674
Yes	14	9	1

Table 5. Eyes at risk for additional CMVR lesions stratified by viremia status in the year previous

Border advancement risk set

- The risk set is all patients who currently have active or inactive lesions
- If a lesion is inactive, borders cannot advance. However, these lesions may become active in between visits and borders may advance
  - In 21 visits, movement occurs when a lesion is labelled inactive or questionnable
  - This implies these lesions became active between visits and became inactive again
- Visits from **380 patients** are considered in this analysis
- Visits are removed with an unknown border advancement measure - 378 patients remain
- Visits are removed that have zero tests in the past year - **350 patients** remain

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Visits/eyes at risk for border advancement

	Viremia in the previous year		
Border advancement	No	Yes	Unknown
No	2340	165	331
Yes	79	40	7

Table 6. Visits at risk for border advancement of CMVR lesions stratified by viremia status in the year previous

	Viremia in the previous year		
Border advancement	No	Yes	Unknown
No	3067	247	459
Yes	85	40	14

Table 7. Eyes at risk for border advancement of CMVR lesions stratified by viremia status in the year previous

Reactivation risk set

- The risk set is all patients who have inactive (or questionnable status) lesions at any point in the study
- However, there are many instances where a patient with an inactive lesion reports border advancement but no activity, which implies reactivation between visits - look for both conditions to create a new reactivation indicator variable
- Also important to specify that the reactivated lesion is not reported as new - that would not constitute an existing lesion
- Visits from **380 patients** are considered in this analysis
- Visits are removed with an unknown reactivation variable measure - 349 patients remain
- Visits are removed that have zero tests in the past year - **325 patients** remain

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Eyes at risk for reactivation

	Viremia in the previous year		
Reactivation	No	Yes	Unknown
No	2894	182	229
Yes	44	14	4

Table 8. Eyes at risk for reactivation of CMVR lesions stratified by viremia status in the year previous

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Mixed effects logistic regression modeling frameworks

outcome = viremia + cd4 + random effect

There are 4 ways to model the random effect:

- Combine eyes per visit per patient (take maximum state between eyes at each visit; events take precedent over non-events)
- Treat eyes as separate units per patient
  - Patient-only random effect
  - Paste ID and eye together so each eye unit is a cluster
  - Nest eye within patient **(preferred)**

CD4 count is a confounder as it is a strong indication of immunosuppression.

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Mixed effects logistic regression results

Data	Random effect	CD4 adjustment OR (95% CI)	CD4 adjustment p-value	No CD4 adjustment OR (95% CI)	No CD4 adjustment p-value
Incident disease					
Combine eyes per patient	Patient only	12.140 (3.411, 43.207)	<0.001	42.423 (12.341, 145.839)	<0.001
Additional lesions					
Combine eyes per patient	Patient only	1.979 (0.856, 4.754)	0.110	1.318 (0.317, 5.477)	0.704
Treat eyes separately	Patient only	2.209 (0.692, 7.055)	0.181	2.332 (0.546, 9.960)	0.253
	Patient/eye clusters	2.363 (0.976, 5.723)	0.057	2.606 (0.573, 11.855)	0.215
	Nest eye in patient	2.153 (0.583, 7.951)	0.250	2.416 (0.544, 10.737)	0.246
Border advancement					
Combine eyes per patient	Patient only	3.069 (1.582, 5.954)	<0.001	4.240 (1.776, 10.125)	0.001
Treat eyes separately	Patient only	1.877 (0.957, 3.682)	0.067	2.013 (0.905, 4.476)	0.086
	Patient/eye clusters	2.283 (1.180, 4.416)	0.014	2.731 (1.191, 6.262)	0.018
	Nest eye in patient	1.955 (0.977, 3.912)	0.058	2.300 (0.996, 5.308)	0.051
Reactivation					
Treat eyes separately	Patient only	1.910 (0.538, 6.783)	0.317	4.145 (1.148, 14.975)	0.030
	Patient/eye clusters	2.066 (0.528, 8.075)	0.297	5.404 (1.446, 20.190)	0.012
	Nest eye in patient	1.951 (0.489, 7.785)	0.344	5.305*	

* - Model did not converge; only point estimate provided

Table 9. Results of mixed effects logistic regression models

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Analysis highlights

Having at least one positive PCR test for CMV viremia:

- increases odds of **incident CMVR** in the following year by a factor of 12.14 compared to those who do not have any positive PCR tests, adjusting for CD4 count (95% Wald CI: (3.41, 43.21), $p < 0.001$)
- increases odds of **additional CMVR lesions** in the following year by a factor of 2.15 compared to those who do not have any positive PCR tests, adjusting for CD4 count and nesting eye within patient (95% Wald CI: (0.58, 7.95), $p = 0.250$)

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Analysis highlights, part 2

Having at least one positive PCR test for CMV viremia:

- increases odds of **border advancement** in the following year by a factor of 1.96 compared to those who do not have any positive PCR tests, adjusting for CD4 count and nesting eye within patient (95% Wald CI: (0.98, 3.91), $p = 0.058$)
- increases odds of **CMVR reactivation** in the following year by a factor of 1.95 compared to those who do not have any positive PCR tests, adjusting for CD4 count and nesting eye within patient (95% Wald CI: (0.49, 7.79), $p = 0.344$)

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Limitations and next steps

All 4 sets of models suggest at the very least a weak association between recent viremia and CMVR events; future amendments and additions to the models will strengthen conclusions:

- Missing data methods (i.e. multiple imputation)
- Bayesian methods (although probably very prior heavy)
- Adjust for HIV viral load, and IV/local therapies
- Weight positive tests for viremia according to recency relative to current visit (time-dependent covariate)

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Questions?

See me for references if interested.

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