1. Organize data

Outcome: Y_{ijk}, i=subject, j=period, k=week

Covariates: ijk treatment, period, week, sequence, viral load, age, gender, ….

2. Three period Cross-over design
   6 sequences, we assume only carry over one period

	μ_A	$\mu_B + \rho_A$	$\mu_C + \rho_B$	Remaining effect	
(1)	A	B	C	ρ_A	ρ_B
(2)	C	A	B	ρ_C	ρ_A
(3)	B	C	A	ρ_B	ρ_C
(4)	B	A	C	ρ_B	ρ_A
(5)	A	C	B	ρ_A	ρ_C
(6)	C	B	A	ρ_C	ρ_B

Notice that ((1)+(4))-((2)+(5))=2(ρ_B-ρ_c)

$H_0: \rho_A = \rho_B = \rho_c \quad \Leftrightarrow \quad H_0: \rho_{AB} = \rho_{AC} = \rho_{BC}$

Generate 3 new sequence indicators:

AB, CA, BC

Sequence 2 = $\begin{cases} 0, & if\ seq = ABC\ or\ BAC \\ 1, & if\ seq = CAB\ or\ ACB \\ 2, & if\ seq = BCA\ or\ CBA \end{cases}$

3. Time variable:

   If you care about one pill is safer than another, only cumulate the 4 weeks in the period;
   If you want to know about specific week, need use week as time variable.

   Treat week as categorical vs continuous?
   Categorical: model nonlinear trend
   Continuous: linear trend

You can plot before model it.

4. Adverse events: often rare events, may not converge.

   To solve :
   1) sum over 4 weeks or code =1 if adverse events occurred at least in one week;
   2) use penalized logistic

Use mixed effects model for this project.