Module E: 

*Developing and testing a viable curative intervention in the clinic*

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Our goal is to first “reduce and control” the virus (a “functional cure”) and then to fully eradicate all virus (a true “cure”).
Detailed studies of “elite” controllers and “post-treatment controllers” suggest that a cure will require

1. low amounts of virus
2. low inflammation
3. sustained T cell responses that reside in tissues, target the right parts of the virus and are primed to attack when the virus rebounds
Stimulating the toll-like receptor (TLR) system

Lower reservoir
Improved T cell responses
Reduce and control

*Enhance immune responses with a goal of reducing and eventually controlling HIV reservoir (a “remission”)*. 

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**Diagram Description**

- **Viremia Peak**
- **Set Point Viral Load**
- **Acute Phase**
- **Chronic Phase**

- **Low T cell response**
- **Medium T cell response**
- **High T cell response**
Shock and Kill

*Enhance immune responses with goal of reducing and perhaps fully eliminating the reservoir (a “cure”)*
Ad26/MVA Therapeutic Vaccination with TLR7 Stimulation in SIV-Infected Rhesus Monkeys

TLR stimulation (with an HIV vaccine) strengthen T cell responses leading to a smaller reservoir and apparent “complete” control of SIV in 3/9 monkeys

Borducci/Barouch, Nature 2016
GS9620: TLR7 agonist in treated HIV disease

• Why are we doing this study?: GS9620 is safe in humans and associated with immune control in monkeys

• What will we do?: Randomized study of GS9620 or placebo followed by treatment interruption

• What do we expect to happen? GS9620 will “supercharge” HIV-specific T cells leading to elimination of virus during therapy and control of what is left after therapy

• Who can participate?: People who partially controlled HIV before starting therapy

• When will this start? January 2017
MGN 1703
TLR9 agonist in treated HIV disease

- **Why are we doing this study?** MGN 1703 stimulates TLR9, induces strong immune responses and is known to be safe
- **What will we do?** Randomized study of MGN 1703 with or without potent HIV antibodies followed by treatment “pause”
- **What might happen?** The combination of MGN 1703/antibodies might shock and kill virus during therapy and control what is left after therapy is stopped
- **Who can participate?** Anyone on stable therapy
- **When will this start?** Summer 2017
Overcoming chronic inflammation
T-cell “activation” is lower in treated than untreated adults, but consistently higher than “normal”

Similar trends consistently observed with multiple measures of inflammation, including IL-6, sCD14, sCD163 and PD-1 expression of T cells

Oncology model: The inflammatory response in cancer tissue stimulates a potent and durable anti-inflammatory response.
Cancer immunotherapy is reshaping a fatal and progressive disease much as antiretroviral therapy reshaped HIV in the 1990s. Most of these drugs are designed to overcome the negative effects of chronic inflammation on immune function.
Anti-inflammatory drugs will also likely be needed

• Several clinical trials are now entering clinic
  – mTOR, IL1β, JAK/STAT, PD-1, CTLA-4, others
• Institute expertise will be used to perform virologic measurements
• By leveraging funded work we will with minimal investment identify those additional therapies that enhance impact of TLR agonists
Developing a combination regimen
Combination strategies will likely be needed to achieve a durable remission.

*The amfAR Institute leverages and complements work ongoing within DARE, the ACTG, the cancer networks (AMC, CITN) and industry.*
UCSF Mission Hall

amfAR Institute for HIV Cure Research Home

Location of HIV research programs, including ARI, Center for AIDS Prevention Sciences, Pacific AIDS Education and Training Center, Global Health Sciences