Why think about antiretrovirals and HIV eradication?

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# Disclosure

<table>
<thead>
<tr>
<th>Relations that could be relevant for the meeting</th>
<th>Company names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employee</td>
<td>Merck Sharp &amp; Dohme Corp., a subsidiary of Merck &amp; Co., Inc., Kenilworth, NJ, USA</td>
</tr>
</tbody>
</table>
HIV/AIDS Continues to Devastate

36.7 million people living with HIV

~20 million may transmit the virus (due to lack of ARV access or lack of viral suppression)

1.8 million new HIV infections in 2017

Approximately 1/3 of people living with HIV don’t know their status

15 million (over 40%) don’t have access to treatment

New infections poised to rise/rising in some populations

UNAIDS, Miles to Go, 2018.
Achieving the Ultimate Goal of HIV Eradication Requires a Multipronged Approach; Antiretrovirals Play an Important Role

Improving antiretrovirals is still critical to addressing treatment, prevention (and persistence?) gaps by
1) addressing tolerability and convenience to maximize adherence
2) optimizing pharmacology to achieve better tissue distribution and forgiveness
Adherence AND Differential Tissue Drug Levels Determine the Effectiveness of HIV Drugs in Prevention (PrEP)

Effectiveness of tenofovir-based prevention increases with consistent use

Trials
- CAPRISA (tenofovir gel, BAT 24 dosing)
- iPrEx
- TDF2
- Partners PrEP (TDF)
- Partners PrEP (TDV/FTC)
- FEM-PrEP
- VOICE (TDF)
- VOICE (TDF/FTC)
- VOICE (tenofovir gel, daily dosing)

Source: Salim S. Abdool Karim/CAPRISA, AVAC Report 2013

Daily oral FTC/TDF in young women in sub-Saharan Africa, efficacy was no different than placebo due to adherence and reduced drug levels in the female genital tract as compared to rectal mucosa

JAMA. 2018;319(12):1261-1268.
## Increased Interest in Long Acting Antiretroviral Agents for Treatment and Prevention

### Table 1  Long-acting antiretroviral agents

<table>
<thead>
<tr>
<th>Mechanistic drug class</th>
<th>Agents</th>
<th>Formulation</th>
<th>Stage of development</th>
</tr>
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<tbody>
<tr>
<td>Nucleoside reverse transcriptase inhibitors</td>
<td>EFdA (MK-8591)</td>
<td>Implant</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>Tenofovir alafenamide</td>
<td>Implant</td>
<td>Preclinical</td>
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<tr>
<td></td>
<td>GS-9131</td>
<td>Implant</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Nonnucleoside reverse transcriptase inhibitors</td>
<td>Rilpivirine</td>
<td>Injectable</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Eltsovifirine</td>
<td>Injectable</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Atazanavir</td>
<td>Injectable</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
<td>Injectable</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Integrase inhibitors</td>
<td>Cabotegravir</td>
<td>Injectable</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Raltegraivir</td>
<td>Injectable</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Entry inhibitors</td>
<td>Ibalizumab</td>
<td>Intravenous</td>
<td>US FDA approved</td>
</tr>
<tr>
<td></td>
<td>PRO 140</td>
<td>Intravenous</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Albuvirtide</td>
<td>Intravenous and subcutaneous</td>
<td>Approved in China</td>
</tr>
<tr>
<td></td>
<td>Broadly neutralizing antibodies</td>
<td>Intravenous</td>
<td>Phase II/III</td>
</tr>
<tr>
<td></td>
<td>Combinictin</td>
<td>Intravenous</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Capsid inhibitors</td>
<td>GS-CA1</td>
<td>Injectable</td>
<td>Preclinical</td>
</tr>
</tbody>
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Abbreviation: EFdA, 4'-ethynyl-2-fluoro-2'-deoxyadenosine.
MK-8591 is a Unique, Highly Potent, Long-Acting Antiretroviral

Potency, pharmacokinetics, and physical properties of MK-8591 enable once-daily, once-weekly, once monthly oral and long acting parenteral administration

- Potent antiviral activity (PBMC EC50 = 0.2 nM)
- Long intracellular persistence (TP T1/2 = 103 hr); exceptional tissue penetration at sites of transmission and replication

Intracellular MK-8591-TP concentrations 30 days after last dose exceed those demonstrated to provide >1 log drop in VL in pH1B studies
MK-8591 Parenteral Formulations Release Effective Drug Levels for >180 Days in Rats and Rhesus Macaques…and Humans

- Low dose amenable to extended-duration parenteral formulation
- >180-day extended release from solid state formulations after a single injection in preclinical species
- Preclinical data suggest the potential to provide coverage for durations up to 1 year
- First-in-human trial of MK-8591-eluting implants demonstrates concentrations suitable for HIV prophylaxis for at least one year Abstract # 484 Tue, 7/23 16:30-18:00
MK-8591 Enriches in Tissues Associated with HIV Transmission and Replication

Relative concentrations of MK-8591 in lymph nodes (sites of HIV-1 replication) are comparatively much higher than observed with other antiretrovirals.

- Potential to decrease low-level replication in tissues during HAART

In healthy subjects, MK-8591-TP levels achieved in rectal and vaginal tissues exceed targets required for efficacy

Grobler CROI 2017; Matthews et al CROI 2018
Achieving the Ultimate Goal of HIV Eradication Requires a Multipronged Approach; Antiretrovirals Play an Important Role.

Improving antiretrovirals is still critical to addressing treatment, prevention (and persistence?) gaps by:
1) addressing tolerability and convenience to maximize adherence
2) optimizing pharmacology to achieve better tissue distribution and forgiveness.
Multiple Studies Provide Evidence for HIV Expression in Lymphoid Tissues in cART-Suppressed HIV+

A. SIV RNA$^+$ cells are mainly in lymphoid tissues

B. HIV DNA$^+$ and RNA$^+$ cells in lymphoid tissues

Other examples:
Fletcher et al., Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues. PNAS 2014.
p24 is Detectable in Rectal Biopsies and Lymph Nodes of cART-suppressed HIV+

p24 detected in 5/7 HIV+ on cART (rectal biopsy samples)

p24 detected in lymph node 7/10 (VL<20) (Total dissociated LN cells)

Collaboration with A. Haase/T. Schacker
Tissue p24 Levels Discriminate HIV status Better than Blood

Rectal p24 (left) and peripheral blood p24 (right) by HIV status

Rectal p24 (left) and peripheral blood p24 (right) by CD4 count in ART-suppressed participants

Blinded studies
Rectal p24 Levels Correlate with HIV-specific CD107a+ CD8s in Controllers on ART

Collaboration with P. Hunt/H. Hatano/USCF labs

**Rectal p24 Levels**

Spearman’s rho: 0.69, P=0.026

% CD107a+ Gag-specific Rectal CD8+ T Cells

Rectal p24 Level pg/10^6 CD4 T Cells

**Rectal HIV RNA**

Spearman’s rho: 0.52, P=0.15

% CD107a+ Gag-specific Rectal CD8+ T Cells

Rectal HIV RNA copies/10^6 CD4 T Cells

CD8s sense HIV proteins

No evidence of an association pre-ART (rho:0.04, P=0.90)
HIV p24 can be detected in GALT samples as well as lymph node biopsies and fine needle aspirates from ART-suppressed HIV+ using ultrasensitive ELISA

In ART-suppressed HIV+, the levels of detected p24 in tissues is greater than that in blood and correlates with immune status

- ART-suppressed immunologic non-responders had significantly higher median rectal p24 levels than immunologic responders

GALT p24 levels in HIV+ on ART were correlated with HIV-specific CD4 and CD8 frequencies in both blood and gut, particularly those that express CD107a in response to Gag peptides

HIV p24 is a marker that should be/appears to be visible to the immune system, yet these cells persist. Does expression drive local immunosuppression/senescence which inhibits immune clearance; analogy to the tumor microenvironment and HBV?

“Fifty percent to 60% of CD3+ T cells did not colocalize with detectable drug concentrations in the gut tissue. In all three species, up to 90% of HIV/SHIV RNA was found to be expressed in gut tissue with no exposure to drug. These data suggest that there may be gut regions with little to no exposure to antiretroviral drugs, which may result in low-level HIV replication contributing to HIV persistence.”
Obstacles to HIV Cure and the Role of Antiretrovirals

Latently infected cells (a)
Clonal proliferation (b)
Persistent viral replication and/or production (c)
Immune privileged sanctuaries (d)
Immune activation, inflammation, compromised gut barrier integrity (e)

Does suboptimal concentrations of ARVs in tissues contribute to antigen/viral persistence, immune activation, homeostatic proliferation and lack of sufficient immune control in tissues?
Therefore, our approaches towards evaluating viral cures have included the demonstrated ability of the drugs to reach sites of latent infection and to do so at significant levels\textsuperscript{18,37,39,43,44}. Notably, the use of molecular tools can permanently eliminate the viral genome and preclude reactivation\textsuperscript{20,21,24,48}. Thus, we suggest that the current successful outcome in achieving this goal in more than 30% of the infected experimental animals reflects the combinatorial use of a suitable animal model, control of viral set points, reach to the viral reservoirs, delivery and intracellular drug penetration of potent LASER ART, and the widespread employment of CRISPR-Cas9 gene editing. The latter enabled high efficiency excision of large fragments of the viral genome from anatomically privileged tissues. Results support the idea that maximal viral restriction must be first established prior to excision to achieve optimal viral editing by CRISPR-Cas9."
Acknowledgements

The MSD HIV Team

Many collaborators...

Rafick Sekaly
Tim Schacker