



# ART AND (HEARING) SCIENCE

Auditory Effects of Antiretroviral Exposure

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# Disclosures and Acknowledgements

1. The content of this presentation is the opinion of the author and does not represent the views of the VA or the United States Government.
2. **Funding**
  - a. Original research presented as a part of this talk was supported by the **American Academy of Audiology Foundation** and **The Ohio State University Alumni Grants for Graduate Research and Scholarship**
  - b. Work on this presentation was supported in part by a VA Rehabilitative Research & Development (RR&D) Service **Merit Review Award (#C0239R)** and with resources and the use of facilities at the **NCRAR (RR&D Center Award #C2361-C)**.
3. **Potential Conflicts of Interest**
  - a. I am a member of the **International Ototoxicity Management Group**, which will be discussed during this presentation.

# + SEMINAR AGENDA

01



**HIV AND ITS  
MANAGEMENT**

02



**AUDITORY  
EFFECTS OF HIV  
& ART**

03



**OTOTOXICITY  
MANAGEMENT**

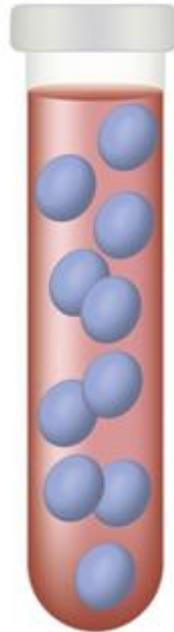
01

# HIV AND ITS MANAGEMENT

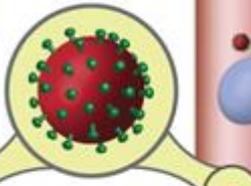
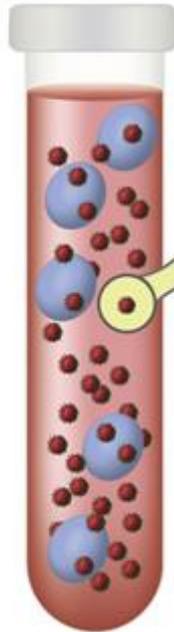


# HIV Progression

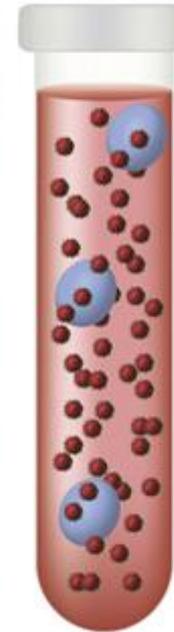
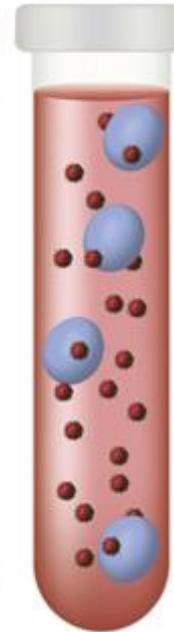
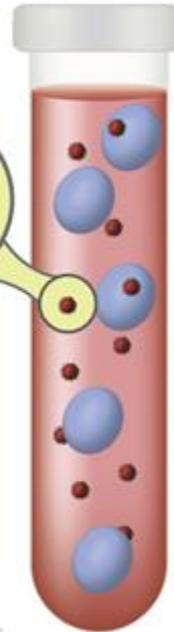
Before HIV Infection



Acute HIV Infection



Chronic HIV Infection



AIDS



Infection

Weeks to Months

Years

CD4 cell

HIV





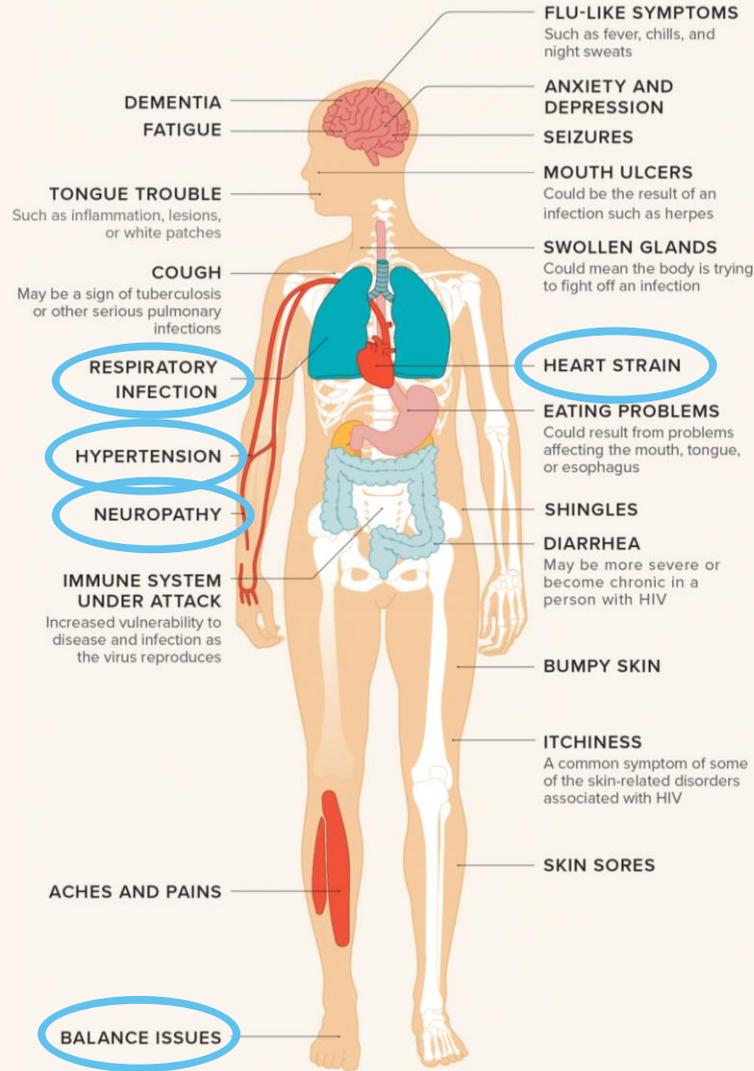
**37.7 MILLION**

people living with HIV globally

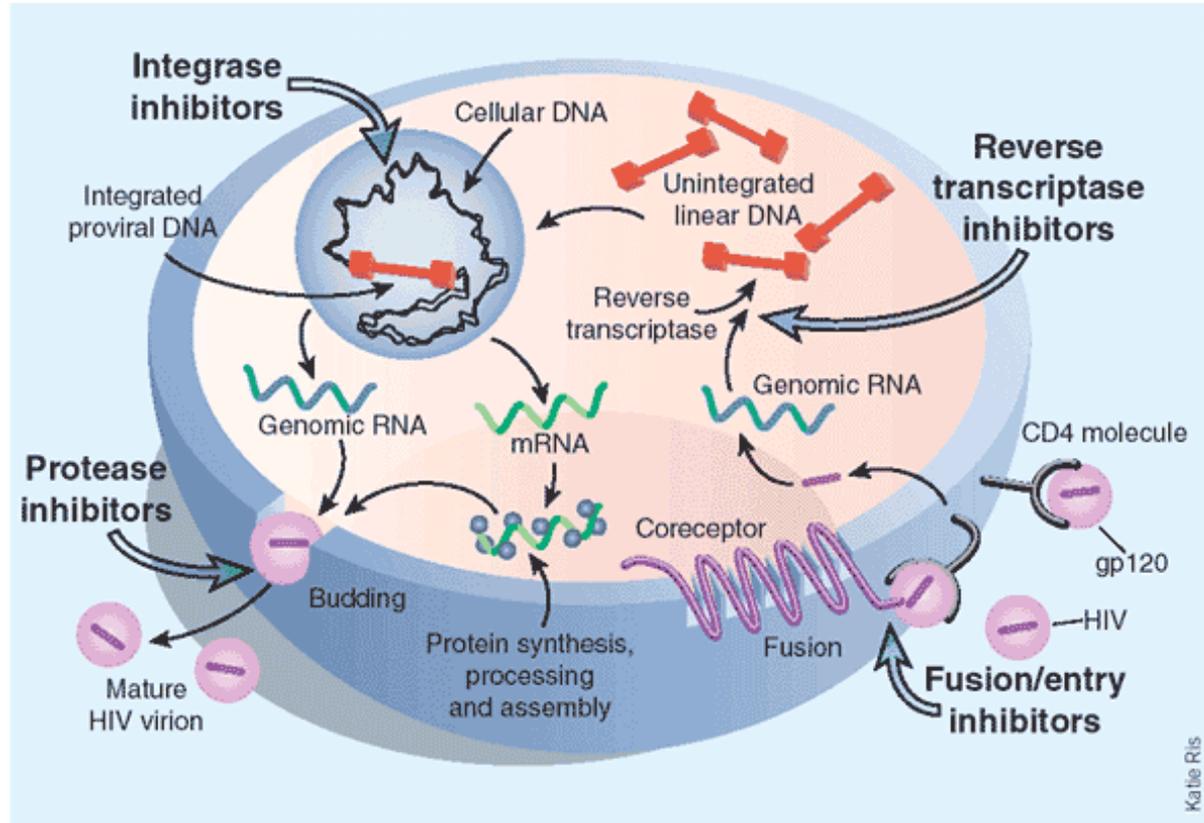
**27.5 MILLION**

people taking antiretroviral therapy

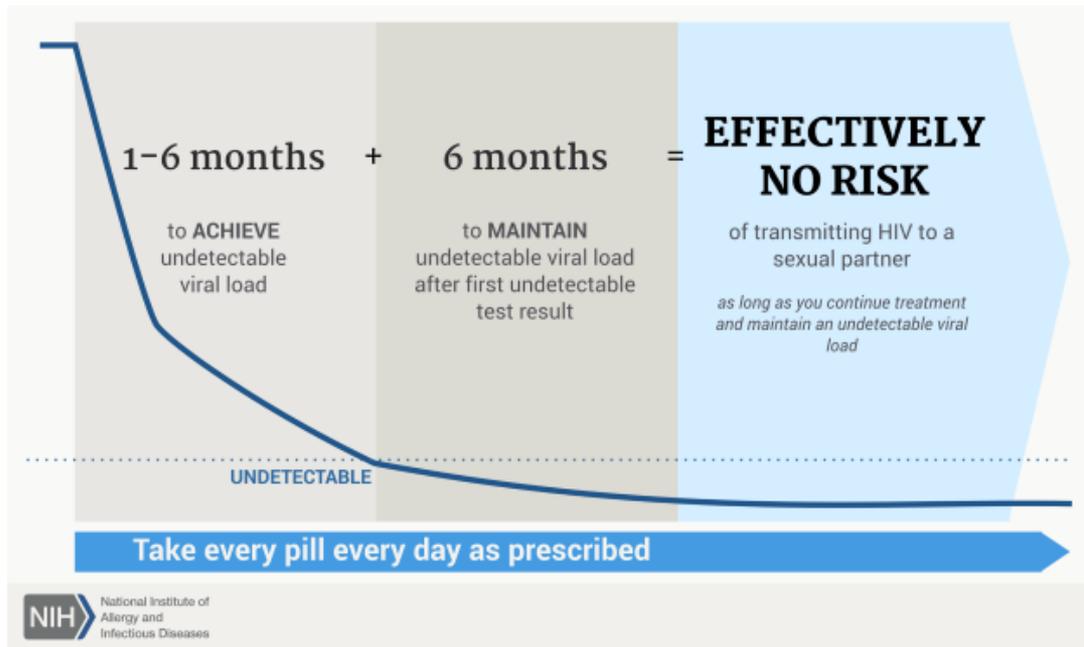
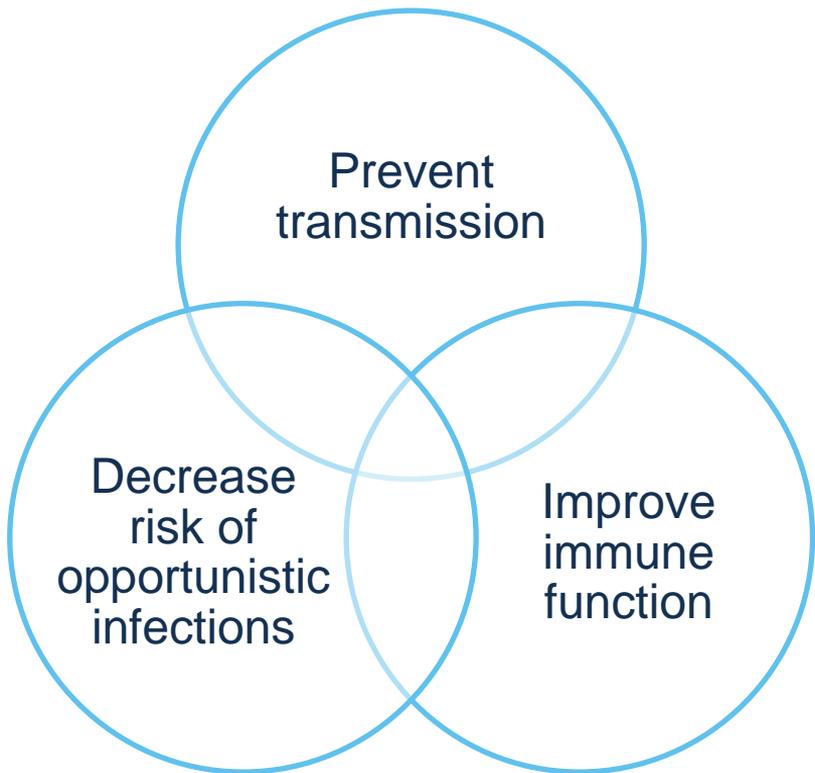
# HIV'S EFFECTS ON THE BODY



# HOW DOES ANTIRETROVIRAL THERAPY WORK?



# WHAT ARE THE GOALS OF ART?



# + COMMON ANTIRETROVIRAL DRUGS



## NRTI

- Emtricitabine
- Tenofovir disoproxil fumarate
- Tenofovir alafenamide
- Zidovudine



## NNRTI

- Doravirine
- Efavirenz
- Rilpivirine



## INSTI

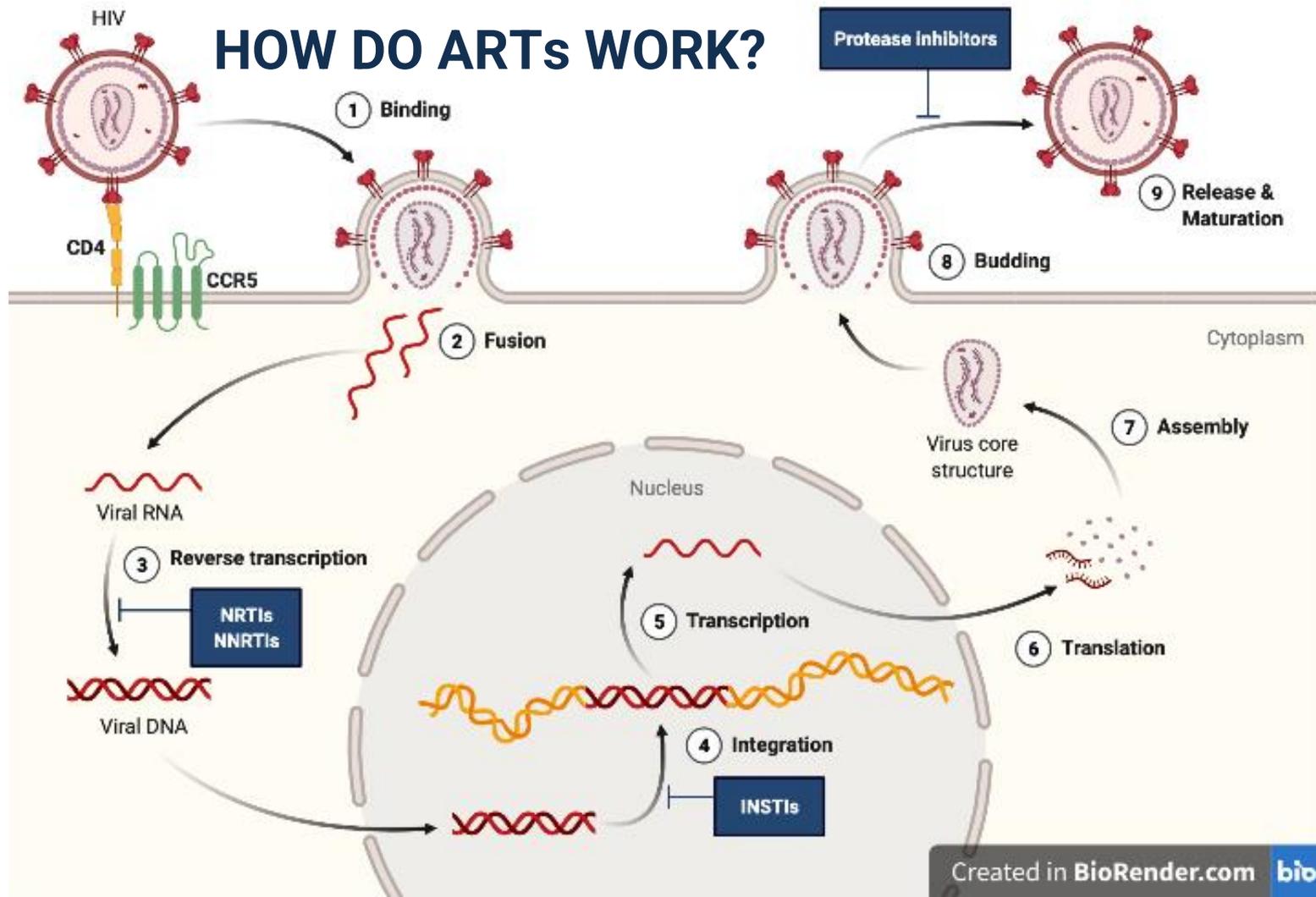
- Bictegravir
- Cabotegravir
- Dolutegravir
- Raltegravir



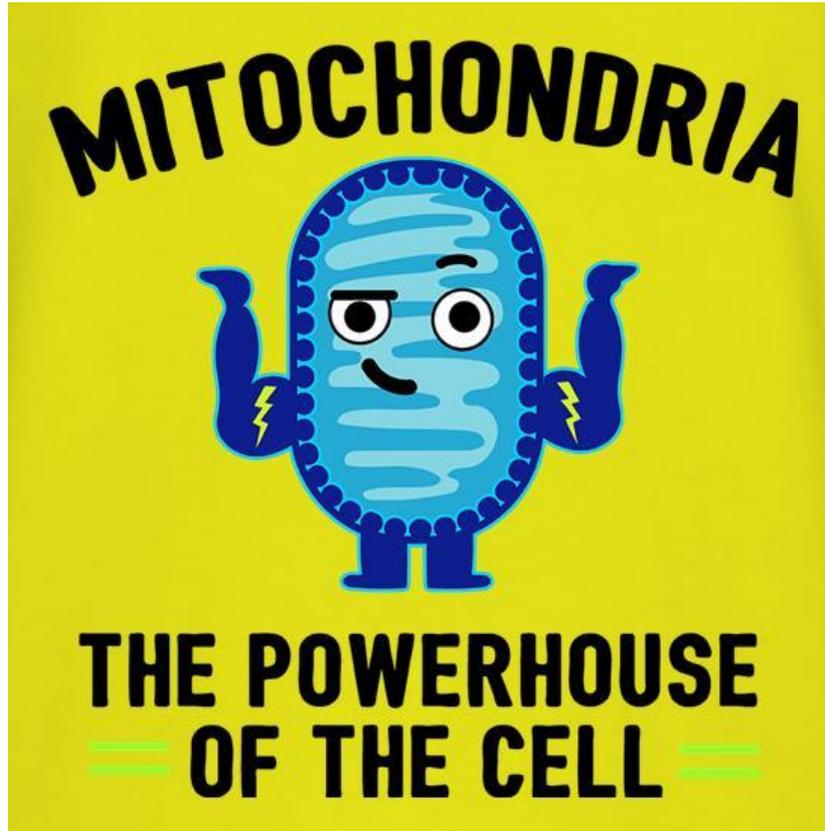
## PI

- Atazanavir
- Darunavir
- Lopinavir
- Ritonavir
- Cobicistat

# HOW DO ARTs WORK?



# ART EFFECTS ON MITOCHONDRIA



1. ARTs disrupts the production of mitochondrial polypeptides and leads to increased ROS production
2. ROS are disruptive throughout the body and exacerbate many conditions, including HL
3. Mitochondrial damage has been shown to drive:
  - Age-Related HL (Kim et al., 2019),
  - Noise-Induced HL (Van Laer et al., 2006),
  - Congenital hearing loss (Kokotas et al., 2007),
  - Ototoxic hearing losses (Estivil et al., 1998; Gurtler et al., 2005).

# + IMPACTS OF ART EXPOSURE DURING PREGNANCY



## COGNITIVE DEVELOPMENT

Variable reports of both global and specific cognitive developmental delays



## LANGUAGE DEVELOPMENT

Increased language delay in ART-exposed children, with greater risk from cART than AZT monotherapy



## AUDITORY FUNCTION

Mixed reports of increased hearing screening failures and auditory dysfunction beginning at birth



# OTHER USES FOR ANTIRETROVIRAL DRUGS



**COVID-19**



**HEPATITIS**

02

## **AUDITORY EFFECTS OF HIV & ART**



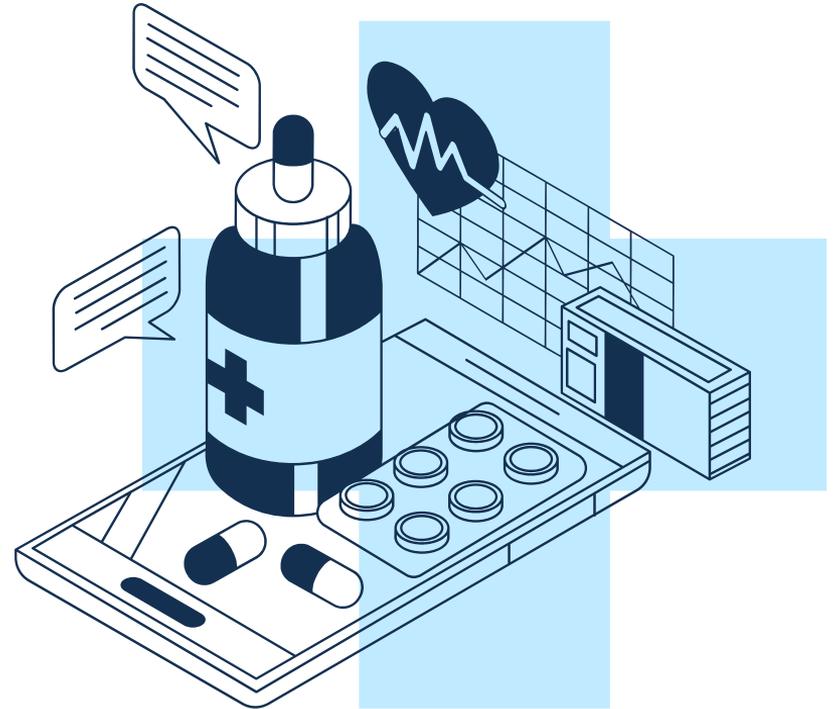


# OTOTOXICITY

Damage to the audiovestibular system as a result of a drug or chemical exposure. Symptoms may include:

- Hearing loss
- Tinnitus
- Balance disturbances

Cochleotoxicity or vestibulotoxicity may be used to refer to toxicity only to the cochlea or vestibular system, respectively.



# AUDITORY IMPACTS OF HIV IN ADULTS

1. Adults with HIV have greater incidence of HL than those without, as measured by both low and high frequency PTA (Torre et al., 2015)
  - a. This is seen across countries, though the incidence varies from 9-26% (Khoza-Shangase, 2018; Matas et al., 2017; Millar et al., 2020; Van der Westhuizen et al., 2013)
  - b. Other groups (Buckey et al., 2019; Torre et al., 2017) report no effects of HIV on auditory thresholds
2. People with HIV had longer ABR Wave I, III, and V latencies, prolonged ABR I-V interpeak latency, and a prolonged P300 latency (Matas et al., 2017)
  - a. Those with AIDS had a decreased middle latency Pa amplitude when compared to HIV and non-HIV groups.
3. Mixed findings related to DPOAE
  - a. Decreased amplitudes over time (Buckey et al., 2019)
  - b. No difference (Torre et al., 2014)



# AUDITORY IMPACTS OF HIV IN CHILDREN



1. Fasanla et al., 2019
  - a. Relationship between HIV viral load and HL in teens
  - b. 20% of teens with HIV had HL



2. Romero et al., 2017
  - a. 86.67% of children exposed to HIV during pregnancy and breastfeeding present with abnormal results on the SSW and 60% abnormal on Simplified Auditory Processing Test

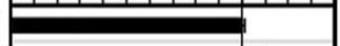
# ART DRUG EFFECTS ON OHCs

## B Cell Viability - 48 hrs

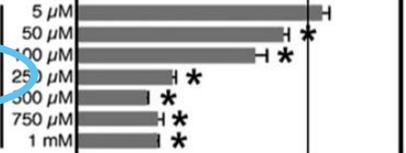
Normalized Values

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1 1.1 1.2 1.3 1.4

Control



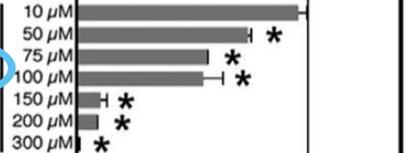
Abacavir



AZT



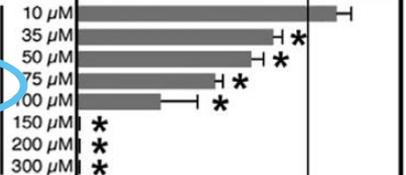
Delavirdine



Didanosine



Efavirenz



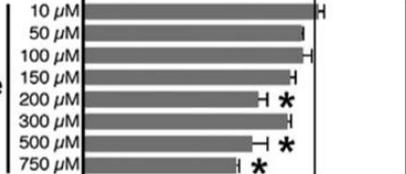
Emtricitabine



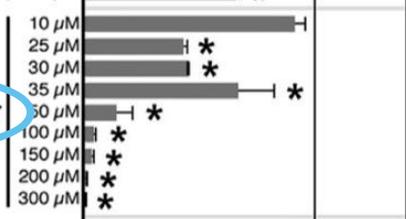
Indinavir



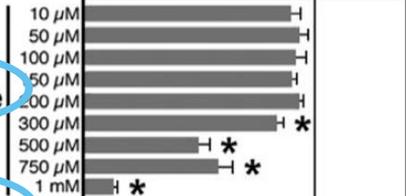
Lamivudine



Nelfinavir



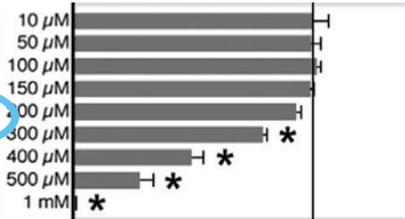
Nevirapine



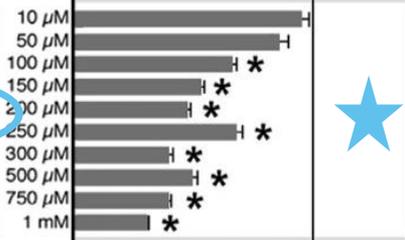
Ritonavir



Stavudine



Tenofovir



Zalcitabine



WHEN YOU SEE A CLAIM THAT A  
COMMON DRUG OR VITAMIN "KILLS  
CANCER CELLS IN A PETRI DISH,"

KEEP IN MIND:



SO DOES A HANDGUN.

# AUDITORY IMPACTS OF ART



1. Marra et al., 1987
  - a. 2.2 OR of HL in pts on ART



2. Bektas et al., 2008
  - a. No differences in ABR or DPOAE threshold after 12 weeks of AZT+3TC exposure

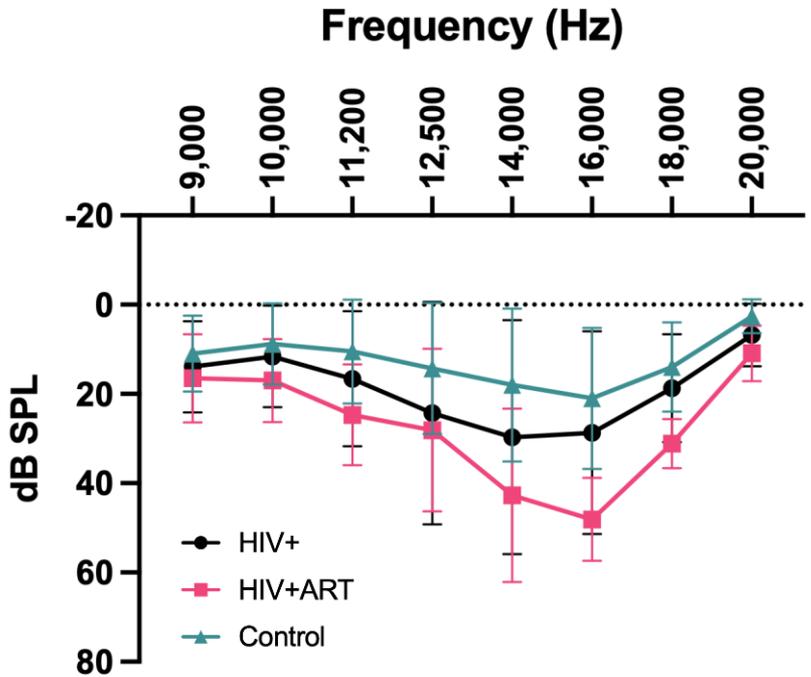
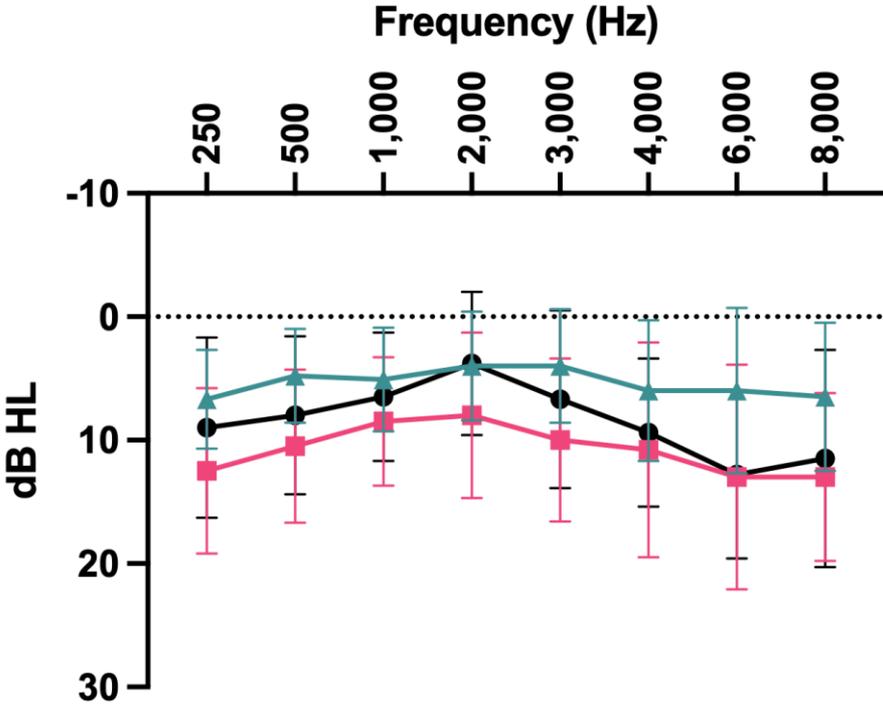


3. Khoza-Shangase, 2018
  - a. More self-reported hearing difficulty after 6 mos of ART



4. Minhas et al., 2018
  - a. TDF+3TC+EFV caused no change in hearing over 6-month period in ART naïve pts.

# AUDITORY IMPACTS OF ART



# AUDITORY IMPACTS OF ART DURING PREGNANCY



1. Poblano et al., 2004

- a. Sig. delays in ABR I latency and I-III interpeak latency for PHEU exposed to AZT or AZT+3TC



2. Fasunla et al. 2014

- a. *in utero* exposure to HIV more likely to result in failed hearing screening and confirmed HL on ABR
- b. Sig. relationship between maternal viral load during pregnancy and HL
- c. Did not control for whether or not mothers were taking ART



3. Fasunla et al., 2018

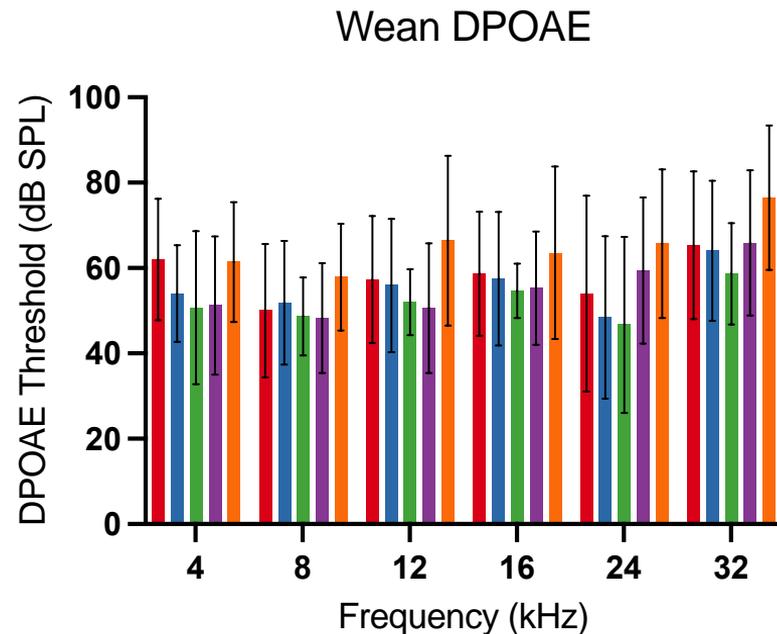
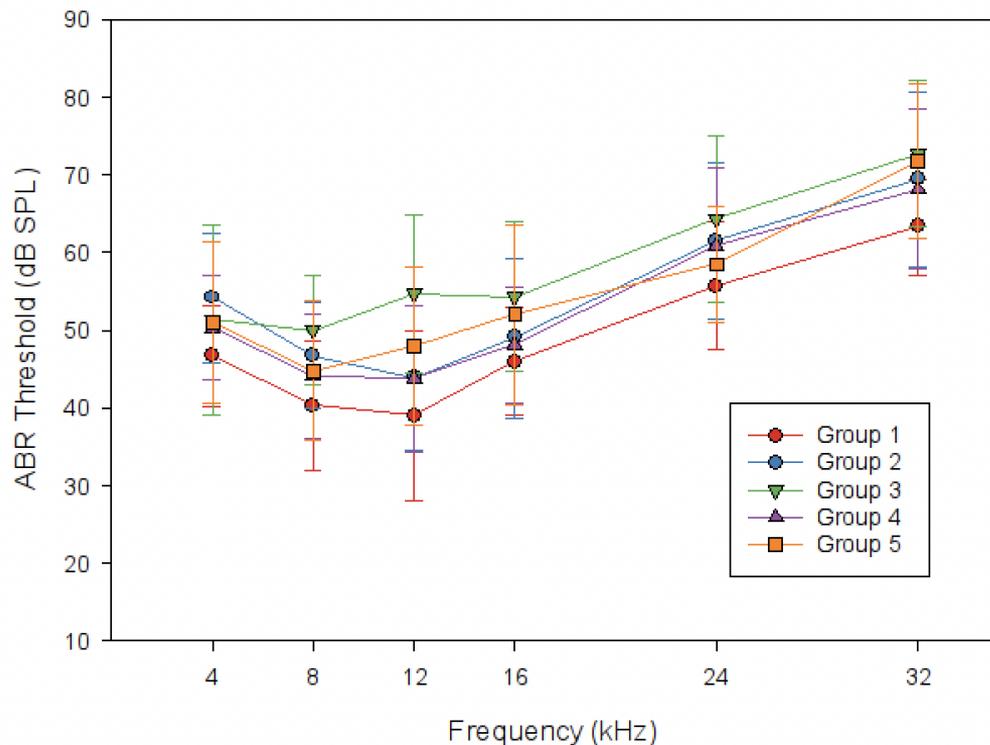
- a. Children exposed to ART *in utero* and born HIV- have higher ABR thresholds at birth than unexposed
- b. Thresholds worsened over first 9 months of life



4. Torre et al., 2017

- a. No specific ART drug was related to an increased likelihood of hearing screening failure using **DPOAE, AABR, or both**
- b. Incredibly wide range of variability in auditory outcomes, even after adjusting for factors like birth weight, gestational age, and other drug exposures during pregnancy
- c. Lower OR for TDF exposure in 1<sup>st</sup> trimester than other ARTs

# AUDITORY IMPACTS OF ART DURING PREGNANCY (PRE-CLINICAL)



# AUDITORY IMPACTS OF ART DURING PREGNANCY



## 1. Torre et al., 2020

- a. PHEU young adults were more likely to have impaired WIN with otherwise normal cognition than HIV+ young adults
- b. Association b/w longer HAART use and impaired WIN in HIV+ young adults

# SYNERGISTIC INTERACTIONS

1. PLWH are at greater risk for opportunistic infections like TB and MRSA (Cenizal et al., 2008) and certain forms of cancer that can be treated with platin-based chemotherapy (Quatan et al., 2005)
2. Multiple factors related to HIV and ARTs suggest that these patients may be at greater risk for HL from these therapies.
3. **Noise** + ART (Bektas et al., 2008)



- a. After 1hr 105 dB SPL noise, higher DPOAEs in ART group than control.  
Still no difference in ABR threshold

4. **Kanamycin** + ARTS (DeBacker et al., in press)



- a. Mice exposed to ARTs during pregnancy and breastfeeding had significantly greater aminoglycoside-induced HL than controls
- b. This difference was worst for animals exposed to cocktails containing tenofovir and efavirenz.

5. **Aminoglycosides** + ART (Harris et al., 2012)



- a. 70% of patients with HIV developed aminoglycoside-induced HL vs. 42% of HIV- patients

03

# OTOTOXICITY MANAGEMENT



# + MONITORING HIV-RELATED OTOTOXICITY



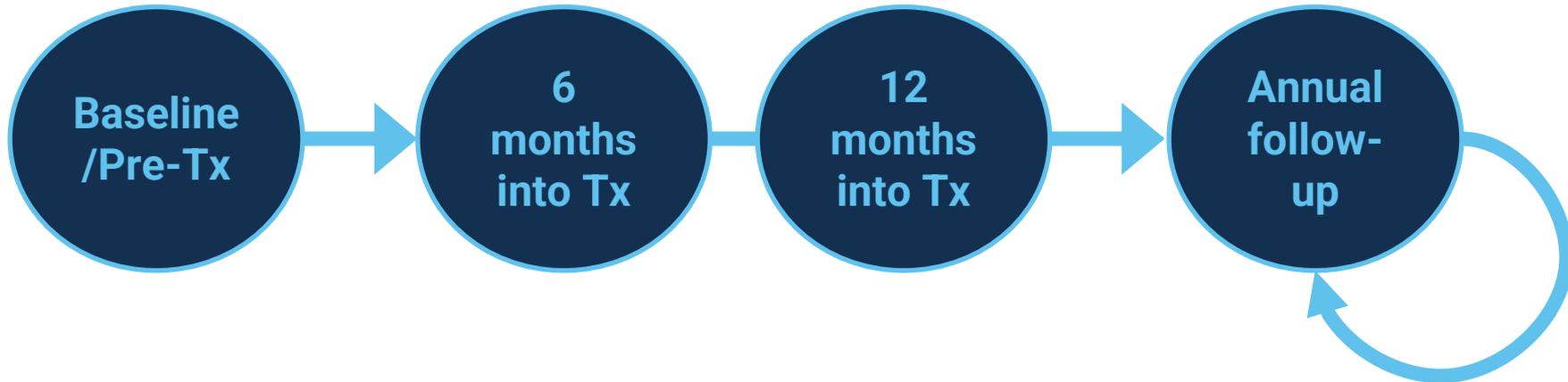
HIGH FREQUENCIES



SPEECH IN NOISE



ABR



# CURRENT OTOTOXICITY MANAGEMENT GUIDELINES

- ASHA, 1993
- AAA, 2013
- HPCSA, 2018



# INTERNATIONAL OTOTOXICITY MANAGEMENT GROUP (IOMG)

Join us!

Learn more and indicate interest at:

<https://go.usa.gov/xzX2g>

**International Ototoxicity Management Group (IOMG)**

**Who are we?**  
We are a global consortium of international stakeholders from universities, task forces, health foundations, professional societies, government agencies and patients created to address healthcare gaps in the clinical management of ototoxicity (hearing loss, tinnitus, and/or balance deficits) caused by medical, occupational or environmental exposures to ototoxicants.

**What is the structure of the group?** For information on current IOMG leadership click here:  
The Coordinating Chair helps identify and align initiatives across focus areas, each managed by its own Chair or Co-Chair.  
IOMG currently has four focus areas targeting: (i) ototoxicity of cancer treatment (chemoradiation therapy), (ii) aminoglycoside-induced ototoxicity (in patients with bacterial infections), (iii) environmental and occupational ototoxicants, and (iv) international considerations.  
A network of formal representatives from external clinical organizations, governmental agencies and patient groups liaise with IOMG to ensure our guidance is contextually relevant and valuable.

**Our mission**  
The IOMG will enhance the social participation and quality of life of millions of individuals worldwide by partnering with patients, healthcare providers and external organizations to address gaps in ototoxicity management thereby giving patients and workers greater control over their long-term auditory and vestibular health.

**What is ototoxicity management?**  
Hearing and vestibular healthcare management centered on individuals at risk for experiencing hearing loss, tinnitus, or balance problems from exposures to ototoxicants  
Includes the identification of at-risk patients, and the diagnosis, routine monitoring, rehabilitation and therapeutic management of hearing and balance deficits in affected individuals

**What is effective ototoxicity management?**  
Ensures that audiology care pathways coordinate with the occupational or medical specialty systems that generate the ototoxic exposure to optimize opportunities for informed consent, early detection, and timely rehabilitation and/or treatment of ototoxicity  
Places the at-risk individual in charge of their own ototoxicity management plan, adapted to their specific needs, priorities, and values (patient centered)

**Why is a global effort needed?**  
Despite the well-established physical, socio-economic, and psychological consequences of hearing and balance dysfunction, clinical practice in these situations is not consistent within or across countries:  
- Few healthcare delivery models integrate ototoxicity management into the essential and/or life-preserving care pathways that utilize therapies that unavoidably increase the risk of ototoxicity  
- There are no standard methods for the auditory surveillance of individuals exposed to hazardous chemicals at work  
A global effort is needed to achieve a global standard of ototoxicity management. A multicultural and interdisciplinary approach is needed to support its application to specific contexts and care pathways development of tools for implementation and health promotion within specific contexts.

**Long-term goals**  
Develop a comprehensive set of clinical guidelines, position statements, and tool kits for implementation and health promotion of ototoxicity management that will address current healthcare gaps in relation to best practices  
Disseminate ototoxicity management materials and toolkits in traditional and non-traditional formats to accommodate specific work environments, healthcare structures, healthcare workers, and patients across the globe

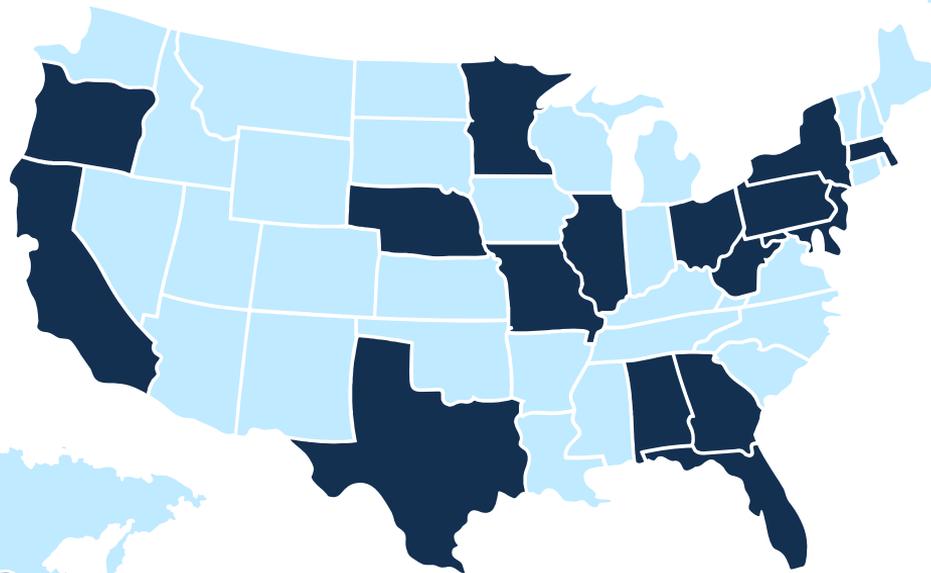
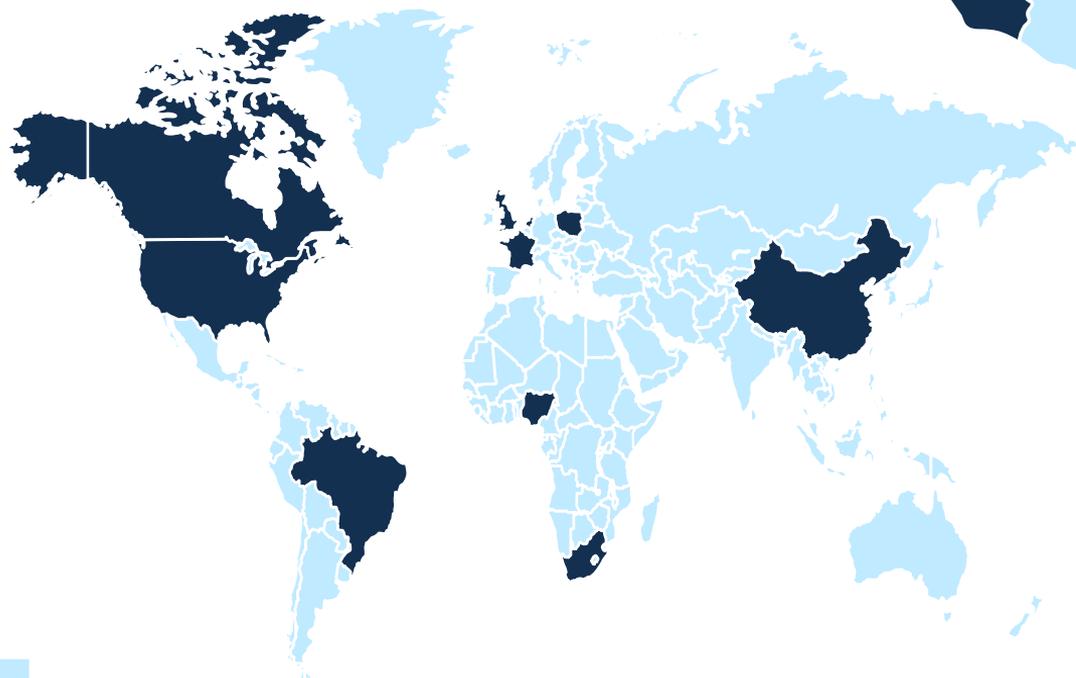
**QUICK LINKS**

- Hospital Locator
- Zip Code
- Health Programs
- Protect Your Health
- A-Z Health Topics





# IOMG MEMBERS



# QUESTIONS?

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