NEED AND ACCESSIBILITY OF NEW TB DRUG REGIMENS

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TREATMENT ACTION GROUP

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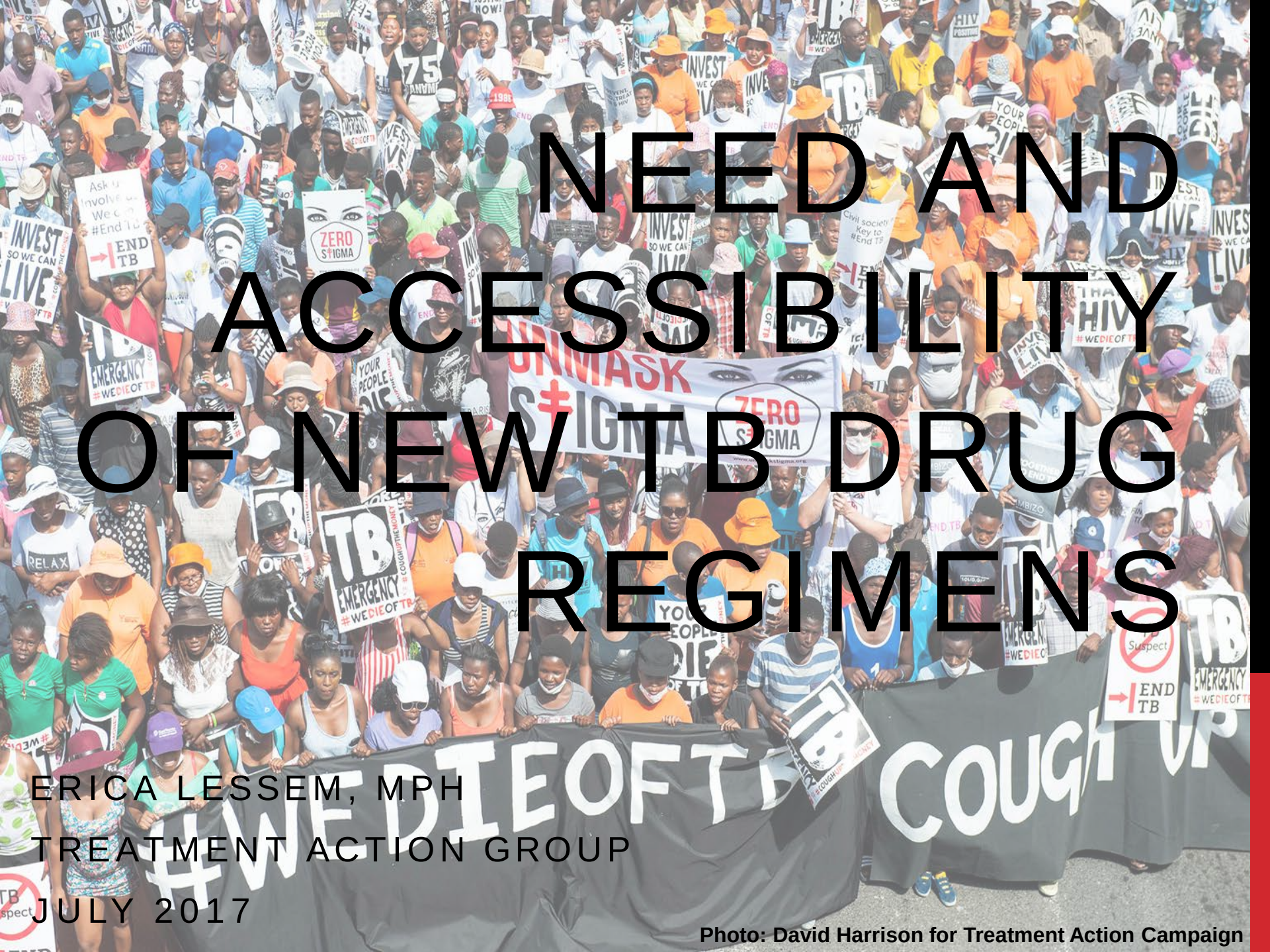
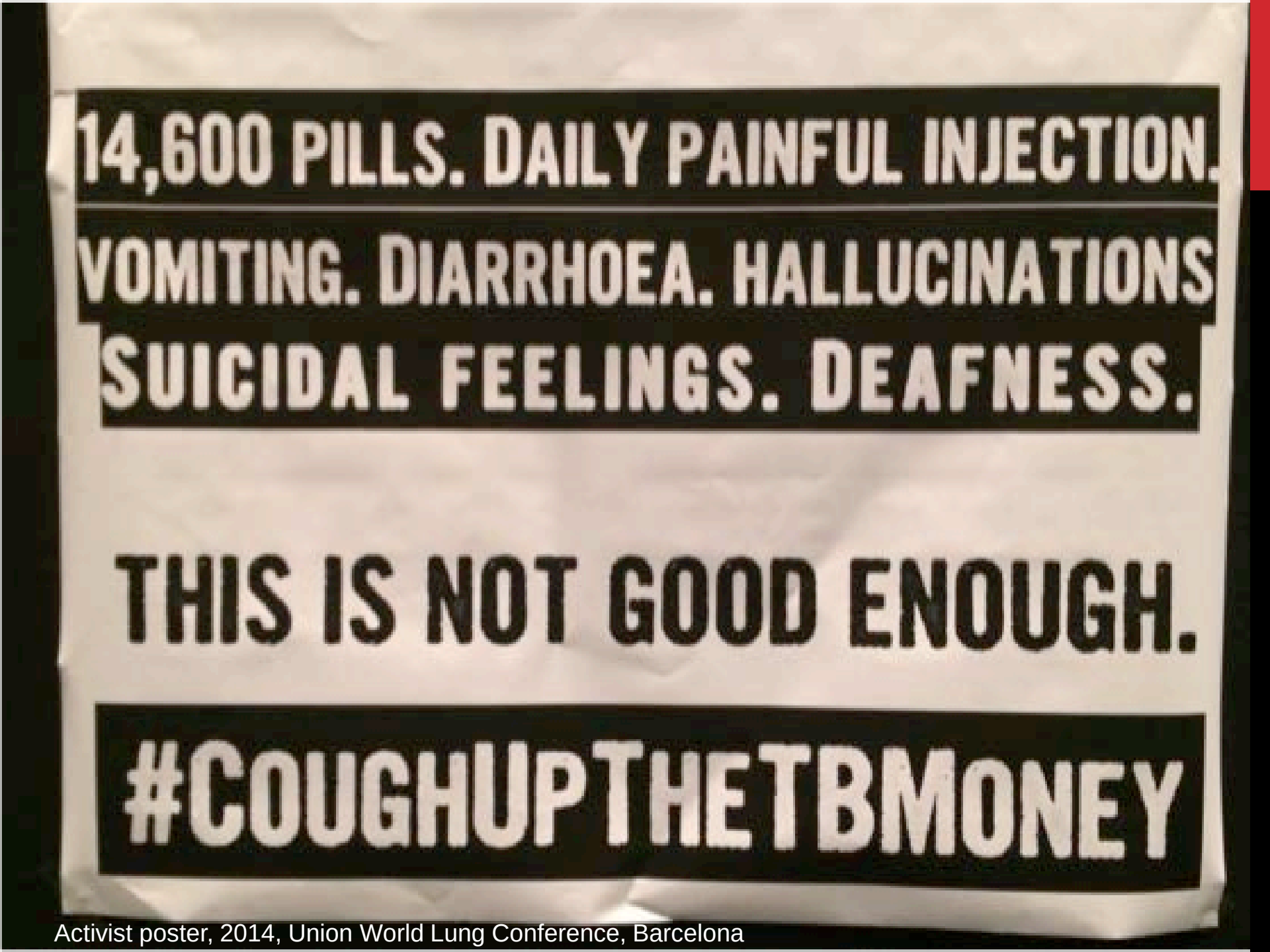


Photo: David Harrison for Treatment Action Campaign

WHY DO WE NEED NEW TB TREATMENTS?



Activist poster, 2014, Union World Lung Conference, Barcelona

TRIAL DESIGN AND REGULATORY CONSIDERATIONS TO GET TO BETTER TREATMENT

OVERARCHING QUESTIONS

- **What is enough information to go into phase III?**
- **When, if ever, is it appropriate to forego a control? Randomization?**
- **How can trials be ethically conducted to gain information about a drug or regimen amidst changing standards of care, and how can adopting new treatments avoid inhibiting important data collection?**
- **How can we avoid perpetuating the current state of insufficient evidence for the drugs/regimens recommended for use?**
- **How to balance urgency of immediate access needs with importance of knowing safety/efficacy profile of drug/regimen?**
- **How can FDA be empowered to hold sponsors accountable for following through on conditions of approval?**

TRIAL DESIGN CONSIDERATIONS

- **Seamless designs**
  - Maximizing efficiency
- **Phase IIC trials**
  - Gathering more data about regimen(s) before exposing many patients/utilizing resources
  - Validating endpoints
- **Endpoints**
  - E.g. adverse event-free, relapse-free cure as a primary endpoint in a superiority trial to improve safety profile while maintaining efficacy
- **Non-inferiority trials and margins**
  - Setting the bar high enough, avoiding a slippery slope
- **Controls**

INCLUSION OF VULNERABLE POPULATIONS

- **We must end systematic exclusion of:**
  - Pregnant women
    - “In the absence of research, each pregnant woman treated for TB becomes an individual experiment” (McKenna et al, CID, 2017)
  - Adolescents and children
    - Orphan Drug Act condones neglect of pediatric research (http://www.treatmentactiongroup.org/tagline/2015/fall/fdas-concession-conundrum)
  - Default must be to include, and provide a rationale for opting out
    - also need pregnancy registry
- **Also need additional research in special populations**
  - People of advanced age
  - People with low CD4 counts
  - People who use drugs/alcohol/opioid substitution therapy

WE ARE HERE TO HELP

Vast experience reviewing protocols / study concepts

- all late-stage MDR-TB trials except Otsuka's
- most late-stage prevention and DS-TB trials

What's routinely missing

- **Plans for results dissemination**
- **Plans for post-trial access**
- **Adequate composition (or even presence) of control arm**
- **Use of non-stigmatizing language in study documents**
- **Appropriate inclusion of key affected groups**

McKenna, et al. Community Advisory Boards on Repeat: What's missing from TB clinical trials protocols? Abstract session 5, TB 2016, Durban, South Africa; 17 July 2016.

REPURPOSING DRUGS: WHAT TO DO IN ABSENCE OF A TB INDICATION?

- **clofazimine**
  - How to ethically gather important safety/efficacy/dosing data, when now part of standard of care, and urgent access needs?
- **linezolid**
  - No clear regulatory pathway for pediatric formulation

ACCESS

PREAPPROVAL ACCESS

- **Important option for patients; allows for more experience with product**
- **Existing expanded access functional in U.S.**
- **Right to Try could do harm without addressing barriers**
- **Could a unified platform streamline process?**

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Expanded Access of Investigational Drugs: The Experience of the Center of Drug Evaluation and Research Over a 10-Year Period

Jonathan P. Jarow, MD[1], **Steven Lemery, MD, MHS**[1], **Kevin Bugin, MS, RAC**[1], **Sean Khozin, MD, MPH**[1], and **Richard Moscicki, MD**[1]
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Results—CDER receives over 1000 applications for expanded access each year. The majority are for single patients, roughly evenly split between emergency and nonemergency use. The vast majority, 99.7%, are allowed to proceed. The incidence of clinical holds for all commercial investigational drug development programs is 7.9%, as compared to only 0.2% related to adverse events observed in patients receiving drug treatments under expanded access.

PRICE HIKES AND SHORTAGES

TB Product	Suppliers	Reason(s) for Shortage (2011–2013)
Isoniazid	Teva, West-Ward (VersaPharm), Sandoz	Lack of raw materials; manufacturing discontinuation; other
Ethambutol	Teva, West-Ward (VersaPharm), Lupin	Manufacturing discontinuation
Injectable rifampin	Bedford, Pfizer, West-Ward (VersaPharm)	Increased demand outpacing supply; other
Capreomycin	Akorn	Manufacturing problems; lack of raw materials; sole-source U.S. manufacturer
Amikacin	Teva, Bedford (discontinuing production)	Manufacturing problems; lack of raw materials; increased demand outpacing supply
Streptomycin	X-GEN	Increased demand outpacing supply
Kanamycin	APP Pharmaceuticals	No longer produced in the United States
Since 2005, the CDC has also received reports of difficulty obtaining isonarif, rifamate, rufabutin, ethionamide, and cycloserine.		

Table from: http://www.treatmentactiongroup.org/tagline/2013/fall/obligatory-overhaul-address-domestic-tb-drug-shortages

PRICE HIKES AND SHORTAGES

The New York Times

The Opinion Pages | LETTERS

What to Do About Drug Shortages

FEB. 17, 2014

- **U.S. product supply vulnerable**
  - 16% of drug shortages for anti-infective drugs (GAO)
- **“low incidence paradox” (CDC); underlying causes unaddressed**
- **FDA needs support/authorization to:**
  - facilitate importation of global, quality-assured medicines to harmonize domestic and global markets
  - enforce shortages reporting
  - create formulary/ list of essential medicines

https://www.nytimes.com/2014/02/18/opinion/what-to-do-about-drug-shortages.html?mcubz=2
http://www.treatmentactiongroup.org/tb/drugs-advocacy/stock-outs/federal-advocacy-meetings/Silent-Crisis

“BE BOLD. MAKE HISTORY. BUT DO IT STRINGENTLY.”

-MARK HARRINGTON

http://www.treatmentactiongroup.org/tb/publications/2012/statement-bedaquiline-fda

JOIN THE MOVEMENT

Researchers, clinicians, and policymakers can also be powerful advocates

Sign up to take action!

http://bit.ly/2rJGKO1

OR

www.treatmentactiongroup.org/tb -- click on the TB Research Action Network link

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