Safeguarding public health

MHRA

Evolving Science of Drug Safety Surveillance:
New Initiatives in Europe

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Current EU initiatives

- **Strengthened methodologies**
  - Streamlined systems, optimal use of spontaneous reports
- **Shift from reactive to proactive**
  - realise the potential of risk management plans
- **Develop research capacity**
  - Infrastructure of centres for drug safety surveillance

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Strengthened methodologies & streamlining systems

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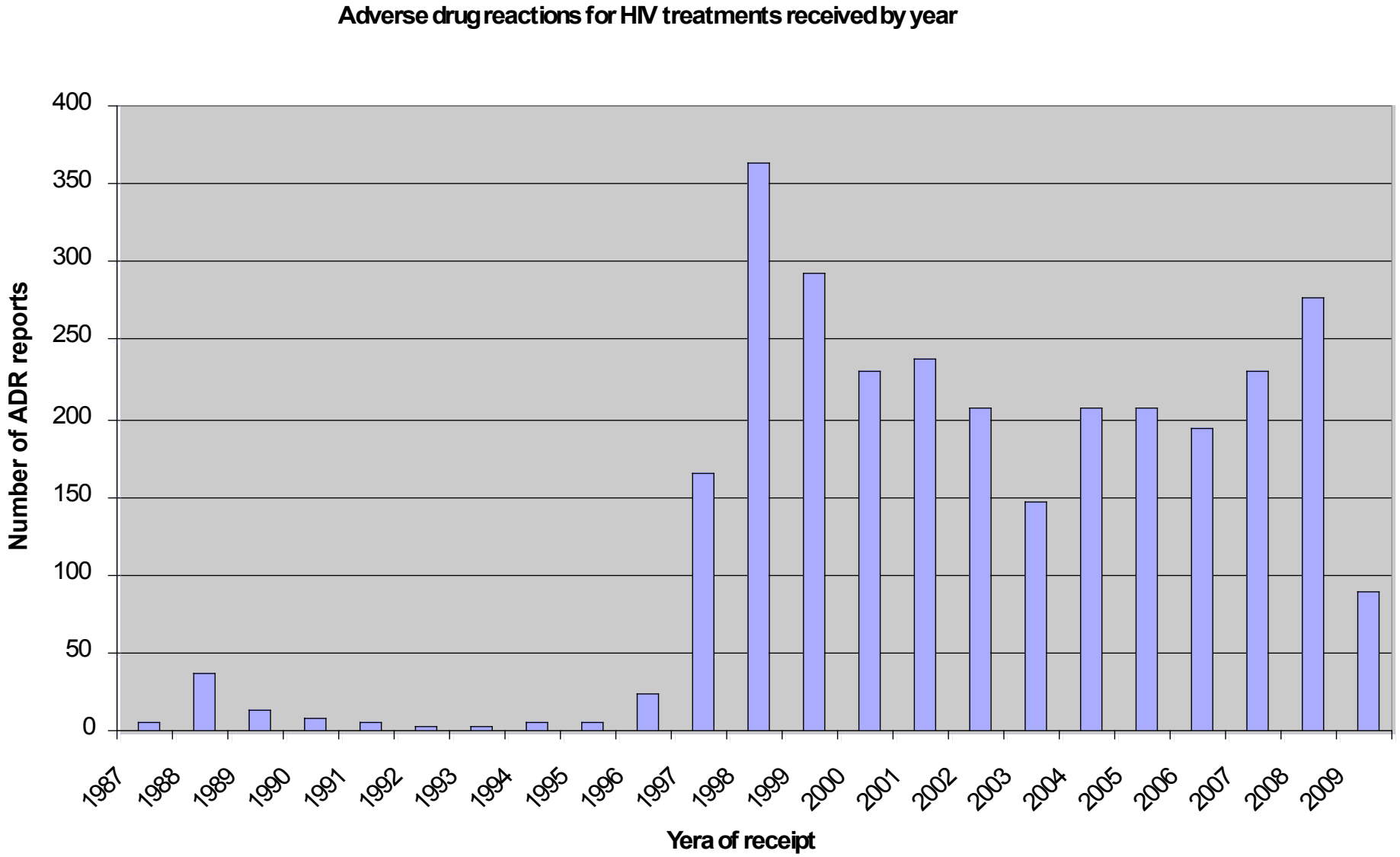
Antiretroviral ADR reporting - UK



Strengthen & streamline

- All ADR reports for EU drugs to single database managed by single data processing network
- Detecting signals from whole EU population 500 million
- Earlier identification of emerging risk

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Regular signal detection

- Weekly assessment of new data in the context of cumulative data
- Systems for measuring disproportionality of reporting (PRRs, EBGMs)
- Earlier detection of new ADRs, or change in frequency/severity of known

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25 May 2010
EMA/319375/2010
Press Office

Press release

EudraVigilance signal detection methods help detect drug safety issues earlier

Adding EudraVigilance statistical signal detection methods to routine drug safety monitoring methods leads to earlier detection of safety issues

An evaluation of the use of the European Medicines Agency's statistical signal detection method in the adverse drug reaction data collected in the EudraVigilance database has shown a significantly earlier detection of drug safety issues in about 54% of cases where a clinically important adverse drug reaction report was found (compared to 'routine' pharmacovigilance).

The study which was published in Drug Safety, the journal of the International Society of Pharmacovigilance, was carried out by the European Medicines Agency and was conducted in relation to centrally authorised medicines. It provides direct evidence for a strong additive role of Eudravigilance signal detection methods. The study also underlines the importance of established pharmacovigilance systems, such as active surveillance, clinical trials or periodic safety update reporting, and concludes that a combination of routine pharmacovigilance and statistical signal detection provides the optimal safety monitoring with earlier detection and better management of safety issues, thereby improving the protection of public health.

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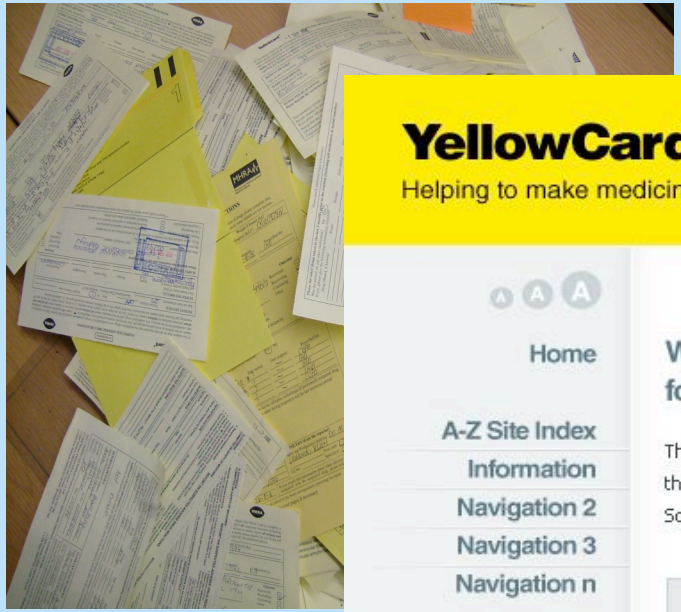
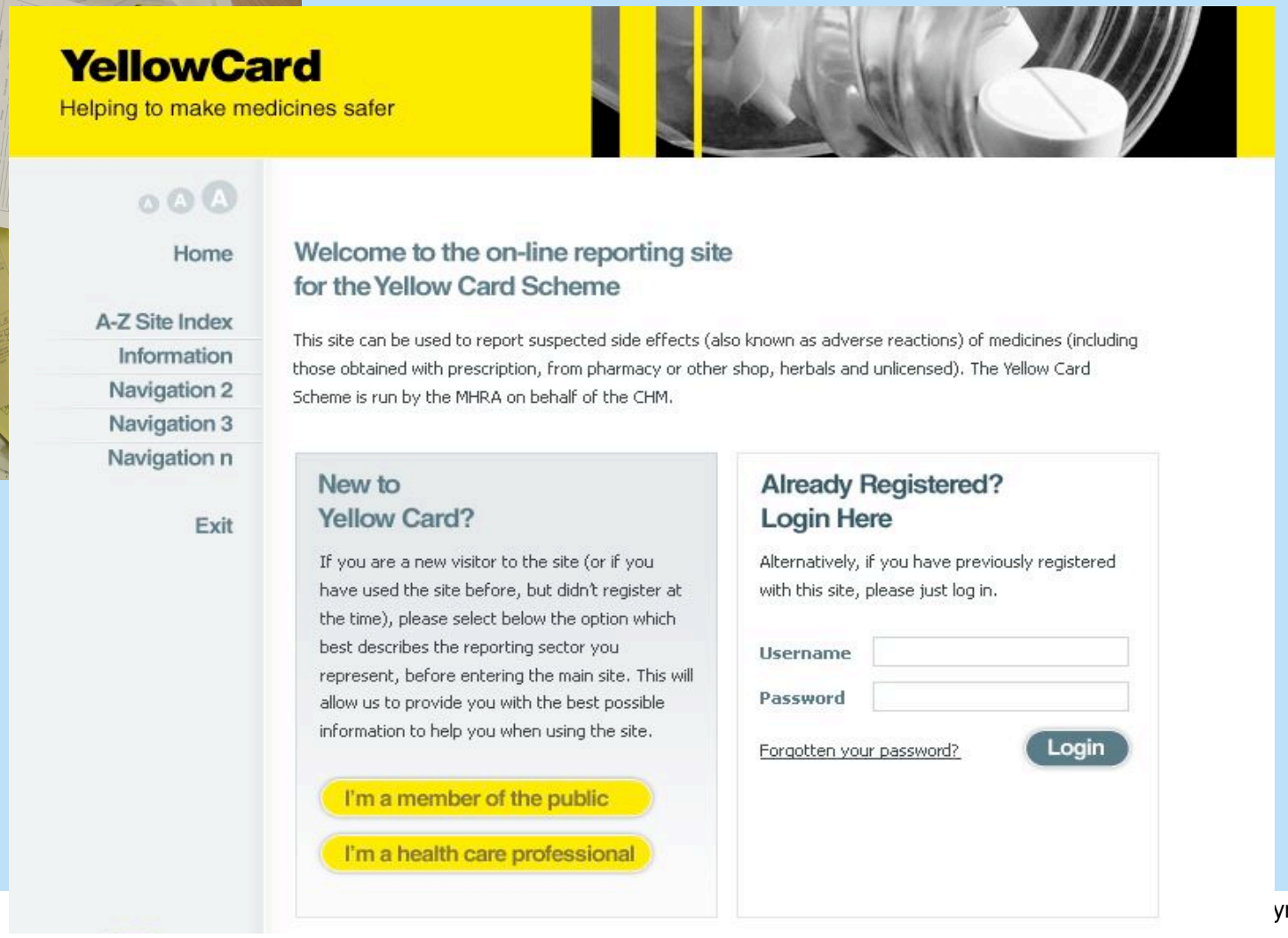
From paper to online reporting





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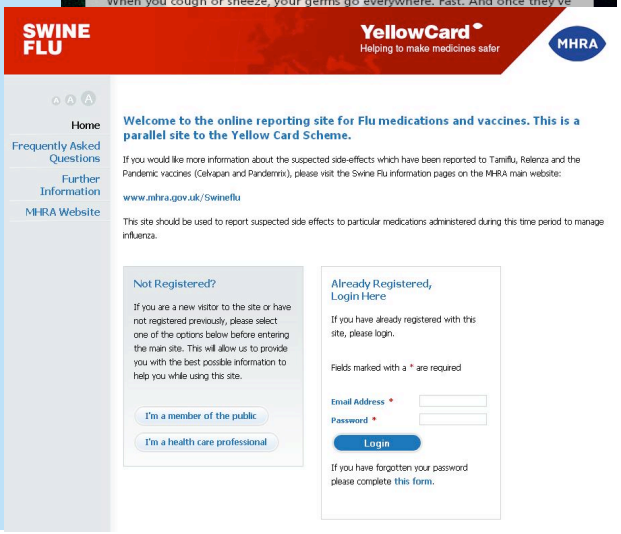
Real-time pharmacovigilance

- Mass vaccination programme
  - 40m doses H1N1 in EU
- UK portal for web reporting of suspected ADRs to pandemic vaccines/antivirals
- Observed/expected calculated for serious events eg Guillain-Barre syndrome
- Signal monitoring three times weekly
- Weekly summaries of safety experience published on website



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From reactive to proactive

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EU Risk Management plans

- Assess expected use of new product in context of indication and expected pattern of use
- Devise strategy to gain knowledge
  (a) about potential signals
  (b) where safety is incomplete even on known ADR
- Risk minimisation measures
- Can request when new issue

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EU pharmacovigilance plans -requests for studies

- 76 (83%) RMPs have proposed studies in the pharmacovigilance plan
- 7 (8%) RMPs may request studies at a later date eg if spontaneous reports are received for a particular reaction
- 8 (9%) RMPs reliant on routine pharmacovigilance alone

Question – which antiretrovirals have RMP studies in place

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Antiretrovirals and RMPs

- **Many Antiretrovirals have EU RMPs**:
  - licensed post 2005, drugs with recent safety issues

- **Examples of activities undertaken to investigate areas of concern:**
  - Clinical studies investigating organ toxicity eg bone with tenofovir
  - Non-clinical studies on aetiology, risk factors for organ toxicity

- **Examples of activities to investigate areas of missing information:**
  - Pharmacokinetic drug-drug interaction studies
  - Clinical studies in special populations, organ dysfunction

- **Examples of risk minimisation measures:**
  - Educational programmes, surveys assessing physician knowledge and practice before and after measure

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Pharmacogenetic studies

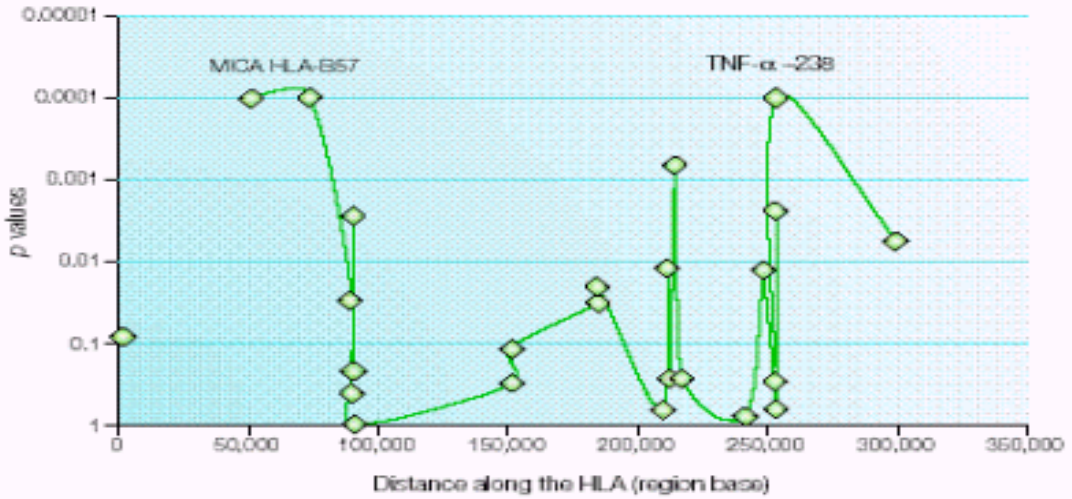

Figure 1 | **Genetic markers in the HLA-B region that are associated with hypersensitivity to abacavir.** The TNF-α –238 and the HLA-B57 polymorphisms were both associated with susceptibility to hypersensitivity. These markers are found to be in close proximity to each other on the same chromosome. Several other intervening markers had varying degrees of positive association. The TNF-α –238 and the HLA-B57 polymorphisms are not within the same linkage disequilibrium (LD) blocks, but show by overlapping patient sets that detection for pharmacogenetics can exceed the LD blocks, which indicates that fewer than 200,000 single nucleotide polymorphisms (SNPs) will be necessary to define SNP profiles. HLA, major histocompatibility complex (MHC) locus; MICA, MHC class I chain-related gene A; TNF-α, tumour-necrosis factor-α.

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Cohort studies

- Copenhagen HIV Programme (**CHIP**): focussed on HIV research: clinical trials and prospective multi-centre cohort studies, such as:

  - **D:A:D cohort** (Data Collection on Adverse events of Anti-HIV Drugs): Set up to study incidence of myocardial infarction. Now monitors other outcomes (diabetes, cancer, renal impairment)

  - EuroSIDA: aims to assess the impact of HIV drugs on the HIV-infected population, has published results on a variety of outcomes (mortality, malignancies, renal impairment)

  Manufacturers of HIV drugs and the European Commission fund D:A:D and EuroSIDA

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Building capacity

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- **ENCePP** = European Network of centres for Pharmacovigilance and Pharmacoepidemiology
- Aim is to facilitate conduct of high-quality, multi-centre, independent post-authorisation studies focussing on safety and benefit:risk
- 60 centres, 8 specialist networks, need to add HIV

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The benefits of ENCePP will be:

- To identify, characterise and promote access to PhVig/Ph Epi resources in Europe
- Improve research standards
- Increase independence and transparency in research
- Stimulate collaboration and exchange of information and experience

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EU Commission drug safety Research Funding

European Medicines Agency

London, 4 August 2009
Doc. Ref. EMEA/497624/2009

Announcement of European Medicines Agency priorities for adverse drug reaction research

At its plenary meeting on 19 March 2009, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted its 2010 priorities for drug safety research based on recommendations from the CHMP's Pharmacovigilance Working Party. The priorities were developed with a view to them being considered as future topics for the 4th Call of the European Commission's 7th Framework Programme (FP7).

On 30 July 2009, the Commission published several calls for proposals of FP7 including three calls under the 'Health' Theme. The priorities for adverse drug reaction research are reflected in the call 'FP7-HEALTH-2010-single-stage', call topic *HEALTH.2010.4.2-3, Adverse drug reaction research* and the European Medicines Agency now wishes to release complementary information with the aim to support researchers in developing proposals that meet the needs of the respective selected research area (please see links below).

Proposals to the call topic *HEALTH.2010.4.2-3: Adverse drug reaction research* should address one of the below areas and more than one project might be funded.

- Long-term effects in children and in young adults of methylphenidate in the treatment of attention deficit hyperactivity disorder (ADHD)
- Long-term adverse effects of immunomodulators (monoclonal antibodies)
- Long-term adverse skeletal effects of bisphosphonates
- Medicine use in pregnancy (design of effective pregnancy prevention programmes, recommendations for safe use in pregnancy)
- Suicidal behaviour in relation to certain drug use (antidepressants, antipsychotics, varenicline, montelukast)
- Safety aspects of antipsychotics in demented patients

Further information on the FP7 calls and specifically on the call 'FP7-HEALTH-2010-single-stage' can be found at http://cordis.europa.eu/fetch?CALLER=FP7_NEWS&ACTION=D&RCN=31090 and http://cordis.europa.eu/fp7/dc/index.cfm?fuseaction=UserSite.CooperationDetailsCallPage&call_id=278.

List of priorities in drug safety research

Duration 5 years

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Innovative Medicines Initiative

- Public Private Partnership
- PROTECT Pharmepi Research on Outcomes of Therapeutics by EU ConsorTium
- Work packages looking at innovative methods, including integration of data on benefit risk

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Summary

- EU initiatives aim for strengthened and streamlined systems, proactive research and capacity building
- Vitally important to share all available evidence on effectiveness and harms internationally
- Effective pharmacovigilance is a public health concern – not just for antiretrovirals

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