Drug Interactions in Clinical Practice

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Declaration of Interests

www.hiv-druginteractions.org & www.hep-druginteractions.org

Receives sponsorship from AbbVie, Merck, BMS, Janssen, Gilead, ViiV.
Editorial content remains independent.
Research funding, travel grants, speakers bureau from Gilead, AbbVie, ViiV, Merck, Janssen
Clinically Significant DDIs

- ARVs have great potential for interactions
  PIs (EVGc) > NNRTIs > MVC > INSTI > NRTIs

- Affects ~20-40% patients on ART

- Patients most at risk
  ≥5 medications
  ≥3 comorbidities (≥3)
  Age >50
  Healthcare silos

- Physicians only correctly identify a third of CSDIs

- Hospital admissions tend to increase, rather than decrease CSDIs
  Major DDIs 13% (admission) vs 18% (discharge)
Guidelines often do not consider Co-morbidities

- Survey of NICE Guidelines for T2 Diabetes, Depression, Heart Failure
- Compared with recommendations from 12 common co-morbidities
- DDI liability assessed

Table 3 | Type of harm expected from potentially serious drug-drug interaction for each index condition

<table>
<thead>
<tr>
<th>Index condition</th>
<th>Cardiovascular*</th>
<th>Bleeding</th>
<th>Renal/potassium</th>
<th>Central nervous system</th>
<th>Other†</th>
<th>Total</th>
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<td>Type 2 diabetes</td>
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<td>27</td>
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<td>Heart failure</td>
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<td>First line recommended drug</td>
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<td>21</td>
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<td>Second line recommended drug</td>
<td>17</td>
<td>34</td>
<td>17</td>
<td>0</td>
<td>22</td>
<td>90</td>
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</table>

*Includes effects on heart rate or rhythm or effects on blood pressure.†Includes myopathy with statin treatment, or clinically relevant altered plasma concentration (for example, of digoxin, lithium, cyclosporin, or theophylline), which might require dose alteration or closer monitoring.

Siobhan Dumbreck et al. BMJ 2015;350:bmj.h949
Traffic Light Summary of DDIs

Liverpool Website Definition:

- Green: No clinically significant interaction, or interaction unlikely
- Yellow: Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration
- Orange: Interaction likely, do not use or use with caution
- Red: No clear data, actual or theoretical

GRADE Equivalent

- Amber
  - Are drugs necessary?
    - Yes: Switch
    - No: Stop

  - Are there alternatives?
    - Yes: Switch
    - No: Stop

  - Can DDI be managed?
    - Yes: Establish Monitoring Plan
    - No: Change dose

  - Accept risk, discuss with patient
Some Highlighted DDIs in 2015

**HIV Therapy**

- DTG and metformin
- Cobicistat vs RTV
- TDF and PIs; any advantage of TAF?
- EFV and levonorgestrel
- ARV-antimalarials
- TB-HIV coinfection
- Chemotherapy and ART
### Guilt by Association - DDI liability largely imputed from RTV

<table>
<thead>
<tr>
<th>Target</th>
<th>Cobicistat</th>
<th>Ritonavir</th>
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<tbody>
<tr>
<td>HIV replication</td>
<td>No activity</td>
<td>PI activity</td>
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<tr>
<td>CYP 3A4</td>
<td>Potent inhibitor</td>
<td>Potent inhibitor</td>
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<tr>
<td>Other CYPs</td>
<td>CYP2D6, minimal effect on CYP2B6</td>
<td>CYP2D6, CYP2B6</td>
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<tr>
<td>PgP</td>
<td>minimal</td>
<td>weak to moderate</td>
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<tr>
<td>Glucuronidation</td>
<td>low</td>
<td>Inducer</td>
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<tr>
<td>Effect on lipids</td>
<td>minimal</td>
<td>moderate</td>
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<tr>
<td>Renal transporters</td>
<td>Creatinine effect</td>
<td></td>
</tr>
</tbody>
</table>
Guilt by Association - DDI liability largely imputed from RTV
But …

RTV can lower exposure of some co-meds through induction of glucuronidation –
- RTV + methadone (methadone AUC↓ 36%)
- RTV + CoC pill (ethinylestradiol AUC↓40-50%)

Cobi causes a significant drop in eGFR
Cobi vs RTV for boosting PIs

ATV

• ATVc (300/150) and ATVr (300/100) were bioequivalent

• RCT (N=692) powered for non-inferiority showed comparable efficacy through 48w
  Significant (but modest) differences in effect on eGFR by w8 (P<0.001)
  No differences in other renal adverse events, hyperbilirubinaemia, nausea

Deeks Drugs 2014 74:195–206
Gallant J Infect Dis. 2013

DRV

• DRV AUC and Cmax were bioequivalent

• DRV Cmin 25-30% lower (DRV/c 800/150 OD vs DRV/r 800/100 OD) - not considered clinically relevant.

• A non-inferiority trial has not been conducted.

Kakuda, J Clin Pharm 2014
‘Boosting’ of Tenofovir and Impact on Renal Safety

**ACTG 5202:**
change in creatinine clearance to Week 96

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in CrCl (mL/min)</th>
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<tbody>
<tr>
<td>ABC/3TC + EFV</td>
<td>+7</td>
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<tr>
<td>TDF/FTC + EFV</td>
<td>+4.5</td>
</tr>
<tr>
<td>ABC/3TC + ATV/r</td>
<td>+5.2</td>
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</tbody>
</table>

No difference in pre-specified renal or bone adverse events between arms

Change in creatinine clearance to Week 48 by TDF Ctrough

<table>
<thead>
<tr>
<th>TDF Ctrough (ng/mL)</th>
<th>Change in CrCl (mL/min)</th>
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<tr>
<td>&lt;40 ng/mL</td>
<td>+5.2</td>
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<tr>
<td>40-90 ng/mL</td>
<td>-2.4</td>
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<tr>
<td>&gt;90 ng/mL</td>
<td>-5.5</td>
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</table>

Sax et al. JID 2011, 204: 1191-1201

Poizot-Martin et al. JAIDS 2013
TDF, bPIs and moderately impaired renal function

**Current dosing recommendations:**

- Mild (eGFR 50-80) – standard dosing
- Moderate (eGFR 30-50) – 300mg q48h
- Severe (eGFR <30) – 300mg twice weekly
- HD – 300mg q weekly (post dialysis)

- Patients with CKD3 (eGFR 30-50)
- Thai (BMI ~ 50)
- TDF 300mg q48h with NNRTI (NVP/EFV) or bPI (LPVr)
- TDF AUC ↑67% with bPI (9.61 vs 5.76 mg.h/L)
- No significant differences in i-c TDF-DP
Tenofovir Alafenamide (TAF, GS-7340)
Novel Prodrug of Tenofovir
TAF vs. TDF: Effect on eGFR

**Events**

<table>
<thead>
<tr>
<th>Events</th>
<th>E/C/F/TAF n=866</th>
<th>E/C/F/TDF n=867</th>
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<tbody>
<tr>
<td>Renal adverse events leading to discontinuation</td>
<td>0</td>
<td>4 (0.5)</td>
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<tr>
<td>Tubulopathy/Fanconi syndrome</td>
<td>0</td>
<td>0</td>
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</table>

Not just a formulation study: TAF dose reduced from 25mg to 10mg with cobicistat

Sax P, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 143LB.
CROI #85LB    Jadelle/Norplant still widely used in LMICs
Expected effect 4-5y, failure rate <1%
48w PK study with EFV (N=20) vs HIV+ not on ART (N=17)
Body weight 59 vs 73kg (known to affect LNG concentrations)
Over 48w, LNG concentrations ↓48%

3 pregnancies within 43-48w
Study was stopped by IDSMB

Note:
• Weight confounder would have ↑ (not ↓) LNG levels
• LNG efficacy target =180pg/mL, but 2/3 women conceived at higher levels
• Swaziland Study (retrospective, N=570) contraceptive failure 0% with NVP and LPVr, and 12.4% with EFV
• What about CoC / progestogen-only pills/ emergency contraception and Mirena?
• What about etonogestrel (2C9/19 and 3A4)?

(no significant PK interaction with NVP [Glasgow 2014])
Effect of HIV on Malaria

**Stable transmission**

**Adults**
- Higher parasitaemias
- More symptomatic (fevers)
- Risk increases with CD4 <200
- Increased risk of placental malaria

**Children**
- No evidence of increased risk

**Unstable transmission**

**Adults**
- More severe disease (OR 2.3)
- Higher fatality (OR 7.5)
- Increased risk of placental malaria

**Children**
- ? Increased severity

Grimwade et al AIDS 2004; Cohen et al. CID 2004;41:1631
Efavirenz and Anti-malarials

What we already know (↑↓AUC)

Co-Artem:  
- LPVr lumefantrine ↑1.96x  
- NVP lumefantrine ↔, Artemether ↓72%  
- ETR lumefantrine ↓13%, Artemether ↓38%  
- EFV lumefantrine ↓56%, Artemether ↓79%  
  1 small study showed antimalarial failure in 4/6 patients

What’s New (CROI #513, #883)

Ugandan kids with malaria, mixed rich (130)/sparse sampling (89)  
- LPVr lumefantrine ↑2.1x, Artemether ↔  
- EFV lumefantrine ↓62%, Artemether ↓59%  
- NVP lumefantrine ↔, Artemether ↓64%

Day 28 parasitological failure  
- Relative risk  
  - EFV >> LPVr (RR 4.4)  
- Absolute risk  
  - LPVr (11%), NVP (32%) EFV (44%)

Malarone ↓ ATQ** with LPVr and EFV, ↓ proguanil with LPVr **  
AQ-AS    EFV contraindicated (↑ LFTs), NVP OK  
No significant DDIs with chloroquine, primaquine, doxycycline

** single dose, HIV- controls
## DDIs between ARVs and Anti-malarials

<table>
<thead>
<tr>
<th></th>
<th>Protease Inhibitors</th>
<th>NNRTIs</th>
<th>Others</th>
<th>NRTIs</th>
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<tbody>
<tr>
<td></td>
<td>ATV/r</td>
<td>DRV/r</td>
<td>LPV/r</td>
<td>EFV</td>
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<tr>
<td>Amodiaquine</td>
<td>(4)</td>
<td>(4)</td>
<td>(4)</td>
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<tr>
<td>Artemether</td>
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<td>Artesunate</td>
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<td>(4)</td>
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<td>(4)</td>
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<td>Atovaquone</td>
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<td>(3)</td>
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<td>CLQ</td>
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<td>Doxycycline</td>
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<td>Lumefantrine</td>
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<td>Mefloquine</td>
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<td>Primaquine</td>
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<td>Proguanil</td>
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<td>Quinine</td>
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<tr>
<td>S / P</td>
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<td>(4)</td>
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</table>

### Quality of Evidence

1. Good
2. Moderate
3. Low
4. Very low
Case

- 40y woman
- HIV+ 2003
- Chronic HCV (genotype 1a)
- Chronic HBV, eAg negative
- Heavy alcohol intake
- uses cannabis, crack cocaine
- NIDDM
- Fibroscan 32kPa (Metavir F4)
- Liver USS – echobright liver, enlarged spleen
- HIV - poor adherence on TDF/FTC/EFV
- Off treatment HIV VL 2.3 x 10^6 copies
- CD4 23 cells/mm3
- Resistance test - wild-type

- HCV RNA 2.3 x 10^5 (log 5.4)
- HBV DNA undetectable
Case

April 2015
- Ascites, grade 2/3 encephalopathy, varices
- Deranged clotting, platelets 40 x 10^9 cells
- Ammonia ↑109umol/L (11-48)
- eGFR markedly declined

Medications:
- Spironolactone
- Bisoprolol
- Lansoprazole
- Metformin
Which ARVs?

- CD4 23 cells/mm³ HIV VL 2.3 x 10⁶
- Spironolactone, bisoprolol, lansoprazole, citalopram, metformin

Safety in Liver and Renal Impairment
Effects of progressive hepatic impairment

**Hepatic cytochromes**

- **CYP2C19**
- **CYP1A2**
- **CYP2D6**
- **CYP 2E1**

**Congugation**

Less affected by liver disease

- Oxazepam
- Lorazepam
- Temazepam

Mainly cleared by glucuronidation

**CLEARANCE**

**Diagnosis**

- Diazepam
- Midazolam

Mainly cleared by CYPs

**CLEARANCE**

**EARLY STAGE**

- CYP2C19
- CYP1A2
- CYP2D6
- CYP 2E1

**INTERMEDIATE STAGE**

- CYP2C19
- CYP1A2
- CYP2D6
- CYP 2E1

**END STAGE**

- CYP2C19
- CYP1A2
- CYP2D6
- CYP 2E1

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Johnson TN et al. *Clinical Pharmacokin* 2010; 49: 189-206
Which ARVs?

- CD4 23 cells/mm3 HIV VL 2.3 x 10^6
- Spironolactone, bisoprolol, lansoprazole, citalopram, metformin

### Safety in Liver and Renal Impairment

<table>
<thead>
<tr>
<th>Liver Impairment</th>
<th>DTG</th>
<th>EVGc</th>
<th>RAL</th>
<th>EFV</th>
<th>RPV</th>
<th>DRVr</th>
<th>ATVr</th>
<th>TDF</th>
<th>ABC</th>
<th>(X)TC</th>
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<tr>
<td>CPT B or C</td>
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### Renal Impairment

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<th>RPV</th>
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<th>ATVr</th>
<th>TDF</th>
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</table>

ND: Not Determined
Which ARVs?

- CD4 23 cells/mm³ HIV VL 2.3 x 10⁶
- Spironolactone, bisoprolol, lansoprazole, citalopram, metformin

Managing Drug Interactions
Dolutegravir + Metformin

- DTG inhibitor of OCT2
- Metformin is excreted unchanged in urine, mainly through OCT2

- Metformin-induced lactic acidosis rare [COSMIC Study; Cryer Diabetes 2003]
- ↑ risk of LA with impaired GFR (<60ml/min; HR 6.37) particularly with high doses (>2g/d; HR 13.0) are also used [Eppenga. Diabetes Care 2014]
- Close monitoring when starting/stopping DTG
- Avoid high Metformin doses (>2g/day), especially in patients with eGFR<60
Which ARVs?

- CD4 23 cells/mm³ HIV VL 2.3 x 10⁶
- Spironolactone, bisoprolol, lansoprazole, citalopram, metformin

Managing Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>DTG</th>
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<td>Bisoprolol</td>
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## Recreational Drugs

### HIV Drugs

<table>
<thead>
<tr>
<th>HIV Drugs</th>
<th>ATVr</th>
<th>DRVrD</th>
<th>LPV</th>
<th>RTV</th>
<th>EFV</th>
<th>ETR</th>
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<th>RPV</th>
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<tr>
<td>Amyl nitrate (poppers)</td>
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<td>Cannabis</td>
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<td>GHB / GBL</td>
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<td>MDMA (Ecstasy)</td>
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### HCV Drugs

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<th>HCV Drugs</th>
<th>OBV/PTV/r</th>
<th>OBV/PTV/r + DSV</th>
<th>SOF</th>
<th>LED/SOF</th>
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Case

- 23y woman from Eastern Europe
- Admitted for vague abdominal pain
- Incidental CXR findings
- Lost to follow up
- Readmitted for TB treatment – HRZE
- HAIN probes suggest resistance to H, R, Z, prothionamide, quinolones and aminoglycosides – confirmed by WGS
- XDR TB diagnosed
Medications

- Bedaquiline
- Pyrazinamide
- Cycloserine
- PAS
- azithromycin
- (intolerant of linezolid)

HIV +
CD4 340, VL 90,000 copies.
No HIV resistance identified.

Potential Drug Interactions?
Interactions with TB medications

**RAL + RIF**
- HIV-: RAL AUC ↓40%, Cmin ↓60%
- HIV+: Rif - ↑variability and exposure
- HIV+: Rif (3x/w) Cmin ↓60%, restored by 800mg Ral bid

**DTG + RIF**
- HIV-: AUC ↓54%, Cmin ↓72%
- DTG 50 bd + Rif gives comparable Cmin as 50qd without Rif

**Dose at 800mg bd (DHHS, BHIVA)**

**Dose at 50mg bd**

Reynolds et al. JAC 2015 Feb;70(2):550-4
# Interactions with TB medications

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<th>EVGc</th>
<th>RAL</th>
<th>EFV</th>
<th>RPV</th>
<th>DRVr</th>
<th>ATVr</th>
<th>TDF</th>
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- Green diamond: No interaction
- Orange dot: Moderately potent interaction
- Red dot: Potent interaction
ART and Chemotherapy

General Principles
• Any ART is better than no ART
• Choose the best chemo regimen, shape ART around that
• Undetectable VL and resistance are less important- can be fixed later
• Start ART early (eg while awaiting histology/staging); try and avoid simultaneous commencement with chemotherapy

Specific considerations
• Avoid ZDV
• If giving nephrotoxic agents (eg platins) monitor patients on TDF, avoid ATV
• Many chemo agents are CYP3A4 metabolised – avoid PIs/cobi if possible
• Beware ATV and chemo eliminated by glucuronidation – eg irinotecan toxicity may ↑↑
• Integrases – generally OK but beware multivitamins from well-meaning dietitians, potential DDI between oxaliplatin and DTG
Poor / Incomplete Medication History

• Large US patient cohort, Sacramento, CA  (N ~2200)

• Ritonavir AND inhaled/intranasal/topical (≥4.5%BSA for ≥1m)
  Identified  =172
  Contacted  = 62
  Lab screen = 34  Cortisol ≤ 4 mcg/dL & ACTH <10 pg/dL
  Hyporadrenalism = 12 (35%)

• Culprits
  Fluticasone (inhaled)  5/8 (63%)
  Fluticasone (nasal spray)  2/5 (40%)
  Budesonide (inhaled)  1/2 (50%)
  Triamcinolone (topical)  2/4
  Beclomethasone (inhaled)  1/5 (20%)
  Mometasone (nasal)  2/7 (29%)

Poor / Incomplete Medication History

- Widespread use of alternative medicines

- Dual casenotes and multiple prescribers
  
  *Discordant in 53% of 100 UK patients*
  
  *(8% potentially having adverse impact)*

- Within hospital
  
  *Incomplete ARV regimen (<3 drugs) in 43% of 83 Tennessee admissions*
  
  *Medication error from non-ID specialists (OR 3.83 [1.08 – 13.54])*

- Between hospital and community
  
  *55% drugs dispensed in community not recorded in HIV casenotes*

Seden et al. BHIVA 2010


Mok et al. Am J Health Sys Pharm 2008;65:55
Summary

- DDIs are frequent, and unavoidable
- DDIs are generally manageable, but only if medication recording is accurate
- Our patients have multiple co-morbidities and characteristics which make harm from DDIs more likely to cause harm, and less likely to be detected
- Need to examine how our healthcare system captures accurate medication histories, and identify significant DDIs

Increases risk of harm
- Fragmented care - information is lost between teams
- Lack of awareness

Protects against harm
- Good communication and training
- Patient involvement
- Exploit digital resources for patient safety
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Laura Dickinson
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Mater Hospital
Jack Lambert